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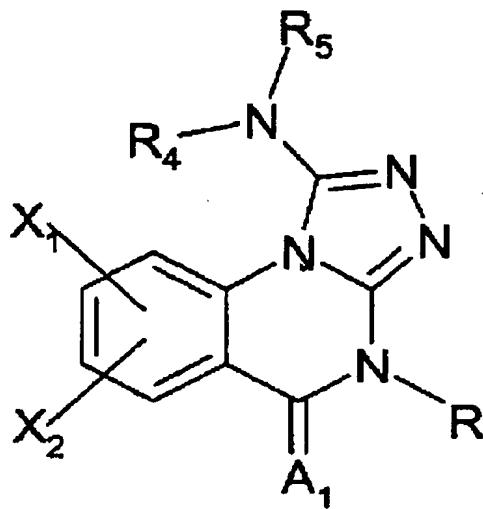
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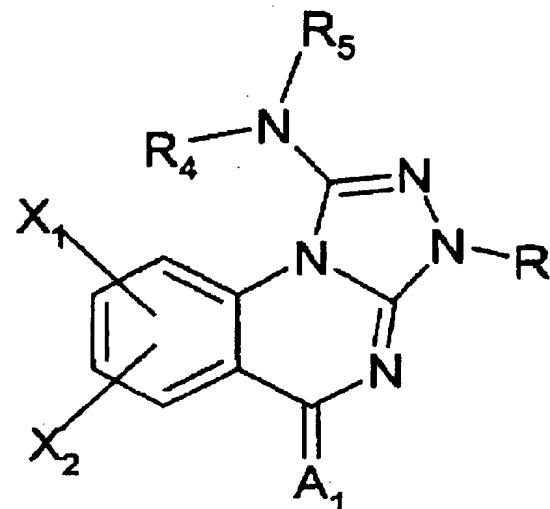
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(54) Titre : 1-AMINO TRIAZOLO[4,3-A]QUINAZOLINE-5-ONES ET/OU -5-THIONES INHIBITRICES DE  
PHOSPHODIESTERASES IV

(54) Title: 1-AMINO TRIAZOLO[4,3-A]QUINAZOLIN-5-ONES AND OR -5-THIONES INHIBITING  
PHOSPHODIESTERASE IV



I



II

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(57) Abrégé/Abstract:

The invention relates to triazolo[4,3-a]quinazoline-5-ones and/or 5-thiones of formula (I) or (II), whereby (I) and (II) are position isomers of group R on nitrogen 3 or 4. Optionally, the invention also relates to the racemic forms, isomers and pharmaceutically acceptable salts thereof. The invention further relates to a method for the production thereof and to compositions containing said derivatives. The compounds act as inhibitors of phosphodiesterase IV (PDE-4).

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(57) Abstract: The invention relates to triazolo[4,3-a]quinazoline-5-ones and/or 5-thiones of formula (I) or (II), whereby (I) and (II) are position isomers of group R on nitrogen 3 or 4. Optionally, the invention also relates to the racemic forms, isomers and pharmaceutically acceptable salts thereof. The invention further relates to a method for the production thereof and to compositions containing said derivatives. The compounds act as inhibitors of phosphodiesterase IV (PDE-4).

1-aminotriazolo[4,3-a]quinazolin-5-ones and/or -5-thiones, inhibiting phosphodiesterases IV

Field of the invention

5 The present invention relates to novel triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones which are useful for the preparation of medicinal products for treating complaints that fall within the domain of a treatment with a phosphodiesterase-4 inhibitor. These medicinal products are useful in particular as anti-inflammatory agents, antiallergic agents, bronchodilators, anti-asthmatic agents or TNF $\alpha$  inhibitors.

10

Technological background of the invention

Cyclic adenosine 3',5'-monophosphate (cAMP) is a ubiquitous intracellular second messenger, which is intermediate between a first messenger (hormone, neurotransmitter or autacoid) and the cellular functional responses: the first messenger stimulates the enzyme 15 responsible for the synthesis of cAMP; depending on the cells concerned, the cAMP then intervenes in a great number of functions: metabolic, contractile or secretory.

The effects of cAMP end when it is degraded by cyclic nucleotide phosphodiesterases, which are intracellular enzymes that catalyse its hydrolysis into inactive adenosine 5'-monophosphate.

20 At least seven major families of cyclic nucleotide phosphodiesterases (PDE) have been distinguished in mammals, numbered from 1 to 7 according to their structure, their kinetic behaviour, their substrate specificity or their sensitivity to effectors (Beavo J.A. *et al.* (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. *et al.* (1994) Molecular Pharmacol. 46, 399-405). The PDE4 enzymes are specific for cAMP.

25 Non-specific phosphodiesterase inhibitor compounds are known, which inhibit several families of enzymes. This is the case for certain methyl xanthines such as theophylline. These compounds have a low therapeutic index, in particular on account of their action on types of PDE present in cells other than the target cells. Conversely, certain families of PDE can be selectively inhibited by various pharmacological agents: the hydrolysis of cyclic nucleotides 30 is slowed down and their concentration thus increases in only the cells in which the type of PDE that is sensitive to the inhibitor is found.

A specific advantage is shown for the phosphodiesterases 4 (PDE4), which have been identified in many tissues including the central nervous system, the heart, vascular endothelium, vascular smooth muscle and that of the aerial pathways, myeloid lines and 35 lymphoid lines.

An increase in cAMP in the cells involved in inflammation inhibits their activation: inhibition of the synthesis and release of mediators in mastocytes, monocytes, polymorphonuclear eosinophils and basophils, inhibition of chemotaxis and degranulation of

polymorphonuclear neutrophils and eosinophils, inhibition of the proliferation and differentiation of lymphocytes.

Cytokines, in particular TNF and interleukins, produced by various types of leukocytes such as the T lymphocytes and polymorphonuclear eosinophils, play an important role in triggering

5 inflammatory manifestations, in particular in response to stimulation by an allergen in the respiratory pathways.

Moreover, cAMP reduces the tonus of the smooth muscle fibres in the aerial pathways; PDE4 inhibitors bring about bronchorelaxation.

Chronic obstructive pulmonary disease (COPD) is a chronic pathology, of slow evolution, which is characterized by obstruction of the respiratory pathways (associated with an inflammation of the respiratory pathways and an elevated neutrophil count). The impairment in pulmonary function is for the most part irreversible (although improvements are possible by treatment with bronchodilators).

The clinical presentation of chronic obstructive pulmonary disease can vary according to the seriousness of the attack, ranging from a simple, non-incapacitating chronic bronchitis to a highly incapacitating condition of the type with chronic respiratory insufficiency. The main clinical characteristics of patients suffering from chronic obstructive pulmonary disease are chronic bronchitis and/or emphysema (associated with an inflammation of the respiratory pathways and/or an elevated neutrophil count).

20 In the course of recent years, selective second-generation phosphodiesterase-4 inhibitors have been proposed as agents that are potentially effective in the treatment of chronic obstructive pulmonary disease (see, *inter alia*, Doherty, *Chemical Biology* 1999, 3:466-473; Mohammed et al., *Anti-inflammatory & Immunodilatory Investigational Drugs* 1999 1(1) :1-28 ; Schmidt et al., *Clinical and Experimental Allergy*, 29, supplement 2, 99-109).

25 Ariflo, a PDE4 inhibitor which is active via the oral route, has been proposed for the treatment of chronic obstructive pulmonary disease (see, *inter alia*: Nieman et al., *Am J Respir Crit Care Med* 1998, 157 :A413 ; Underwood et al., *Eur Respir J* 1998, 12 :86s ; Compton et al., *Am J Respir Crit Care Med* 1999, 159 :A522. See also the oral account by Compton given at the meeting of the "European Respiratory Society" held in Madrid on 12

30 October 1999, as well as that by Torphy and Underwood at the 4<sup>th</sup> world conference on inflammation, held in Paris from 27 to 30 June 1999. Ariflo is currently under study, in phase III clinical trials, for the treatment of chronic obstructive pulmonary disease.

However, it should be pointed out that Ariflo has a number of drawbacks. Specifically, significant undesirable effects, such as nausea and vomiting, have been reported after 35 administration of a dose of 20 mg as a single intake (see Murdoch et al., *Am J Respir Crit Care Med* 1998, 157 :A409). The appearance of undesirable effects at such low doses will limit the use of Ariflo and will prevent the use of daily single-dose pharmaceutical forms, thus leading to discomfort for the patient.

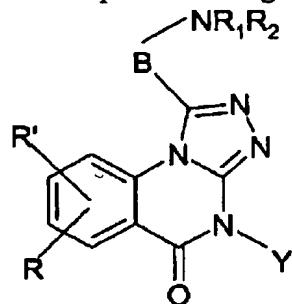
Osteoporosis is a disease characterized by a decrease in bone mass and the loss of skeletal architecture, thus leading to bone fracture. A large number of post-menopausal women suffer from this disease and the number of patients is continuing to grow.

5 Two different types of bone cell exist: osteoblasts, which participate in the formation of bone; and osteoclasts, which play a role in bone resorption. More particularly, the bone mass results from the sum of the formation of bone by the osteoblasts and the resorption of bone by the osteoclasts. Consequently, molecules which inhibit the bone resorption induced by the osteoclasts are effective in the treatment of osteoporosis. Calcitonin,  
10 biphosphonates and, quite probably, oestrogens are agents for combating resorption and are used clinically. Molecules which stimulate the formation of bone by the osteoblasts also constitute agents that are promising in the treatment of osteoporosis (see also Yoshihiro et al. Jpn. J. Pharmacolog. 1999, 79, 477 – 483).

15 Extensive research has been carried out in recent years to obtain and develop powerful PDE4 inhibitors. This turns out to be difficult due to the fact that many of the potential PDE4 inhibitors are not without activity on the phosphodiesterases of other families.

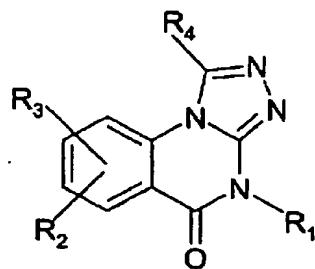
At the present time, the lack of selectivity of PDE4 inhibitors represents a major problem, given the extent of the functions regulated by cAMP. There is thus a need for powerful and selective PDE4 inhibitors, i.e. inhibitors which have no action with respect PDEs belonging  
20 to other families.

European patent EP 0076199 describes compounds having the following general formula:



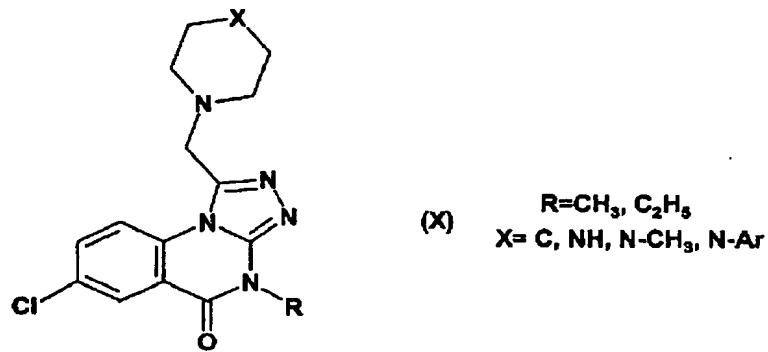
25 in which R and R', which may be identical or different, represent H, halogen, C<sub>1-3</sub> alkyl, alkoxy or nitro; Y represents an alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, aryl or aralkyl group and B represents (CH<sub>2</sub>)<sub>n</sub> with n = 1, 2, 3 or CH(CH<sub>3</sub>). These compounds are proposed for use in the treatment of asthma, bronchitis and allergic disorders.

Patent DDR 158 549 describes compounds having the following general formula:



in which R<sub>1</sub> represents H, alkyl or aryl; R<sub>2</sub> and R<sub>3</sub> represent H, alkyl, halogen, OH, SH, O-alkyl or S-alkyl; R<sub>4</sub> represents H, alkyl, haloalkyl, OH, SH, O-alkyl, S-alkyl, SO<sub>2</sub>-alkyl, NH<sub>2</sub>, SCN, aryl or (CH<sub>2</sub>)<sub>n</sub>COOalkyl and n = 0 to 2. These compounds are proposed for use  
5 as diuretics and anti-anaphylactic agents.

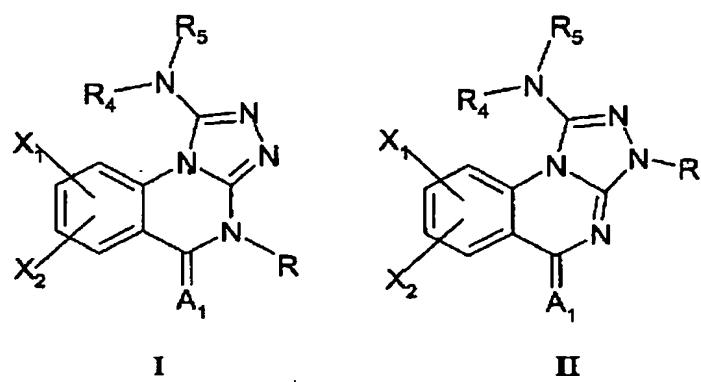
In J. Prakt. Chem., 1990, 332(5), 629-39, Ram et al. describe compounds having the following formula:



10 These compounds are proposed for use in treating hypertension.

#### Summary of the invention

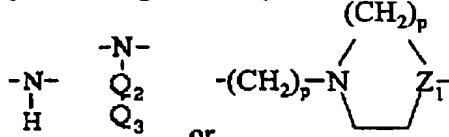
15 The invention relates to triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones of formula I or II :



I and II being positional isomers of the group R on nitrogen 3 or 4, in which:

- $A_1$  is O or S ;
- $X_1$  and  $X_2$ , which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano or carboxyl,
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, which are optionally substituted with one or more halogen atoms,
  - $-CO-Q_1-Q_2-Q_3$  in which:

-  $Q_1$ - is: a single-valency bond,  $-O-$ ,

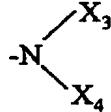


10 , or , in which p is an integer which can range from 0 to 3 and  $Z_1$  is CH, N, O or S;

-  $Q_2$ - is:

- a)  $-(CH_2)_q-$ , q being equal to 0, 1, 2, 3, or 4, or
- b)  $-(CH_2-CH_2-O)_r-$ , r being equal to 2, 3, or 4, and

15 -  $Q_3$  is: -H, -OH, lower alkoxy,  $-O-CO-X_3$ ,  $-NHX_3$  or



in which  $X_3$  and  $X_4$ , which may be identical or different, represent a lower alkyl group, it being possible for  $X_3$  and  $X_4$  to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N,

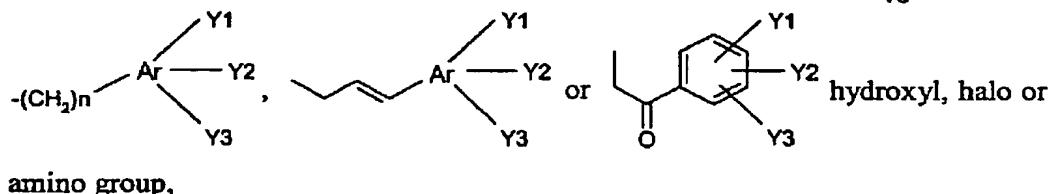
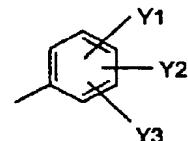
20 -  $-NH-R_1$  in which  $R_1$  represents a lower alkyl group, optionally substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and  $-CO-Q_1-Q_2-Q_3$ , or

-  $-NR_2R_3$  in which  $R_2$  and  $R_3$ , which may be identical or different, represent a lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$  groups, it being possible for  $R_2$  and  $R_3$  to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and  $-CO-Q_1-Q_2-Q_3$ ;

25 30

- R represents:
  - lower alkyl, lower alkenyl, lower alkynyl, arylalkynyl or 2-, 3- or 4-pyridylalkyl

optionally substituted with a lower alkyl, a lower alkoxy, a



5 in which:

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N,
- Y1, Y2 and Y3, which may be identical or different, represent:
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen,  $-\text{NHR}_1$ ,  $-\text{NHR}_2\text{R}_3$ ,  $-(\text{CH}_2)_s\text{CN}$  or  $-(\text{CH}_2)_s\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$  in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or  $-\text{S}(\text{O})_m\text{R}_8$  in which m is 0, 1 or 2 and  $\text{R}_8$  is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms; and

10

15

-  $\text{R}_4$  and  $\text{R}_5$ , represent:

20

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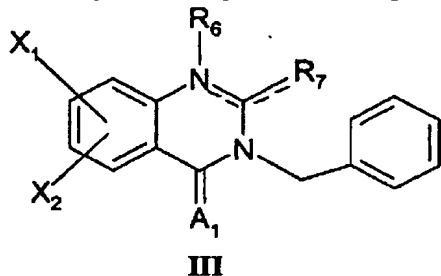
- lower alkyl when  $\text{R}_4$  and  $\text{R}_5$  are identical, or aralkyl, cycloalkyl or cycloalkylalkyl when  $\text{R}_4$  and  $\text{R}_5$  are different,
- lower alkyl, it being possible for  $\text{R}_4$  and  $\text{R}_5$  to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or  $\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$ , it also being possible for two of the atoms in the ring thus formed to form part of another ring chosen from phenyl or heteroaryl comprising from 4 to 8 carbon atoms including 1 to 4 hetero atoms;

and optionally the racemic forms and isomeric forms thereof, as well as the pharmaceutically acceptable salts thereof.

The compounds of the present invention are useful as inhibitors, in particular as selective inhibitors, of the phosphodiesterase enzyme, and more particularly the enzyme PDE4.

5 The invention also relates to compounds used mainly as intermediates in the synthesis of the compounds of formula I or II.

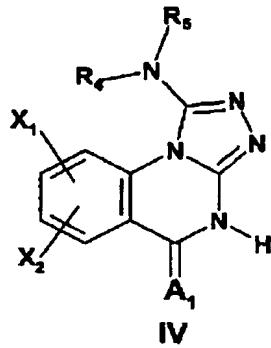
A first series of intermediates comprises compounds having the general formula III below:



in which:

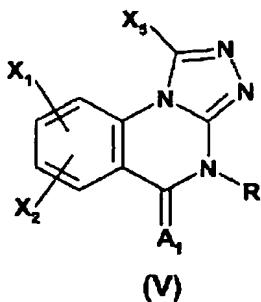
10 -  $X_1$ ,  $X_2$  and  $A_1$  are as defined above;  
- the dashed lines represent optional double bonds;  
-  $R_6$  is hydrogen; and  
-  $R_7$  is S or hydrazino;  
it being possible for  $R_7$  to be linked to the nitrogen at  $R_6$  to form a ring, particularly a  
15 triazole, optionally substituted with a lower thioalkyl, mercapto or halogen group.

A second series of intermediates comprises compounds having the general formula IV below:



20 in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above.

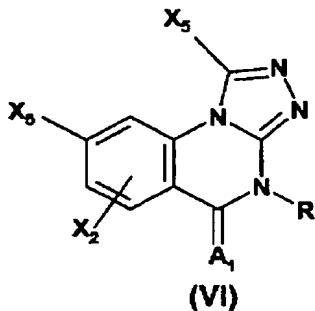
A third series of intermediates comprises the compounds having the general formula V below:



(V)

in which  $X_1$ ,  $X_2$ ,  $A_1$  and  $R$  are as defined above and  $X_5$  is a halogen, particularly F, Br or Cl, or an  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group.

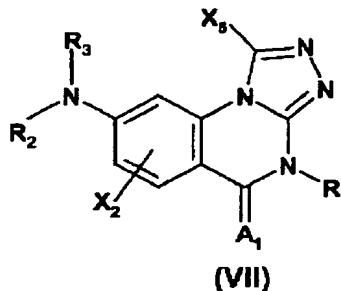
5 A fourth series of intermediates comprises compounds having the general formula VI below:



(VI)

in which  $X_2$ ,  $X_5$ ,  $A_1$  and  $R$  are as defined above.

10 A fifth series of intermediates comprises compounds having the general formula VII below:

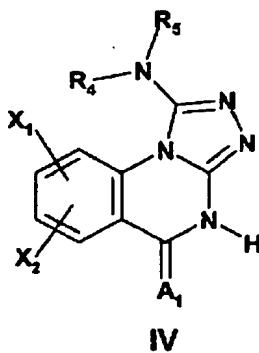


(VII)

in which  $X_2$ ,  $A_1$ ,  $R_2$  and  $R_3$  are as defined above,  $X_5$  is a halogen, particularly F, Br or Cl, or an  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group.

15

The invention also relates to a process for manufacturing compounds of formulae I and II. The process is characterized in that it comprises the reaction of a compound of general formula IV:



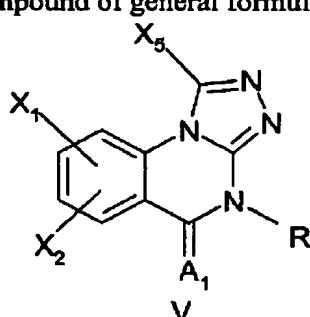
IV

in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above,  
with a compound of general formula

$R-X'$

5 in which  $R$  is as defined above and  $X'$  is a halogen, particularly F, Br or Cl, or an  $-OCOX_7$ ,  
or  $-OSO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group;  
in order to obtain a mixture of compounds of general formulae I and II which are then  
optionally separated.

10 The compounds of general formula I can also be prepared by a process characterized in that  
it comprises the reaction of a compound of general formula V :



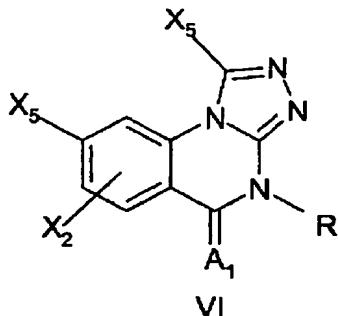
V

in which  $X_1$ ,  $X_2$ ,  $A_1$  and  $R$  are as defined above and  $X_5$  is a halogen, particularly F, Br or  
Cl, or an  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group;

15 with a compound of general formula:

$HN R_4 R_5$

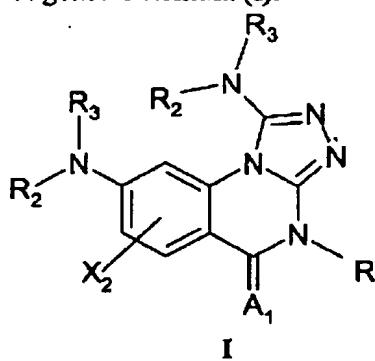
in which  $R_4$  and  $R_5$  are as defined above,  
in order to obtain a compound of general formula I.  
When  $X_1$  is  $-NR_2R_3$  and  $-NR_2R_3$  and  $-NR_4R_5$  are identical, the compounds of formula I  
20 corresponding to this definition can be obtained in particular by reacting a compound of  
general formula VI:



in which  $X_2$ ,  $X_5$ ,  $A_1$  and  $R$  are as defined above,  
with a compound of general formula:

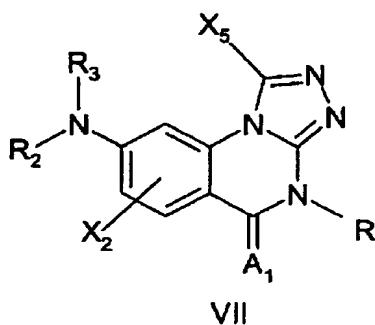


5 in which  $R_2$  and  $R_3$  are as defined above,  
in order to obtain a compound of general formula (I):



I

When  $X_1$  is  $-\text{NR}_2\text{R}_3$  and  $-\text{NR}_2\text{R}_3$  and  $-\text{NR}_4\text{R}_5$  are different, the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula VII:

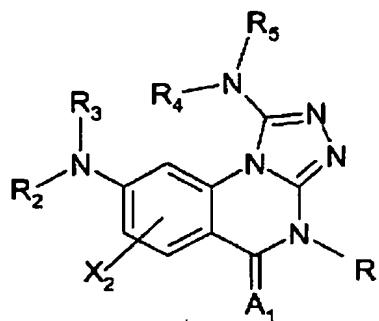


VII

in which  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R$ ,  $R_2$  and  $R_3$  are as defined above,  
with a compound of general formula :

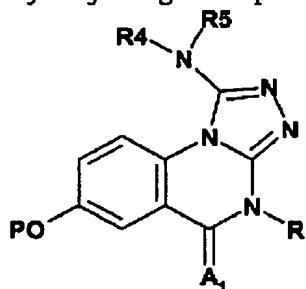


15 in which  $R_4$  and  $R_5$  are as defined above,  
in order to obtain a compound of general formula (I):



I

When  $X_1$  is H and  $X_2$  is OH, the compounds of formula I corresponding to this definition can also be obtained in particular by subjecting a compound of general formula Ia<sub>1</sub>:

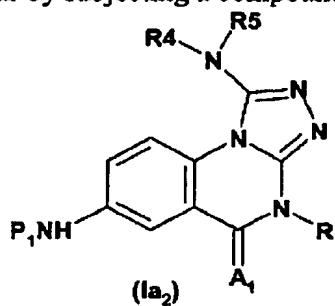


(Ia<sub>1</sub>)

5 in which  $A_1$ , R,  $R_4$  and  $R_5$  are as defined above and P is a protecting group, to conditions allowing the removal of the protecting group P in order to obtain a compound of general formula I.

When  $X_1$  is H and  $X_2$  is NH<sub>2</sub>, the compounds of formula I corresponding to this definition

10 can also be obtained in particular by subjecting a compound of general formula Ia<sub>2</sub>:

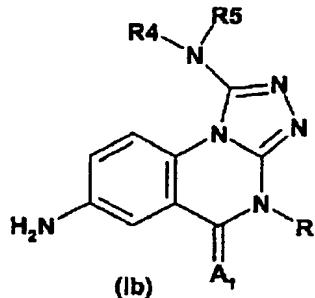


(Ia<sub>2</sub>)

in which  $A_1$ , R,  $R_4$  and  $R_5$  are as defined above and  $P_1$  is a protecting group, to conditions allowing the removal of the protecting group  $P_1$  in order to obtain a compound of general formula I.

15

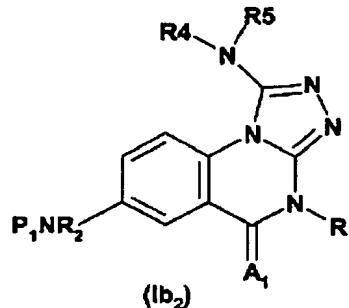
When  $X_1$  is H and  $X_2$  is  $NHR_2$  in which  $R_2$  is as defined above, the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula Ib :



5 in which  $A_1$ , R,  $R_4$  and  $R_5$  are as defined above,

with a compound of formula  $R_2X_5$  in which  $R_2$  and  $X_5$  are as defined above, in order to obtain a compound of general formula I.

10 Furthermore, when  $X_1$  is H and  $X_2$  is  $NHR_2$  in which  $R_2$  is as defined above, the compounds of formula I corresponding to this definition can also be obtained by subjecting a compound of general formula Ib<sub>2</sub> :

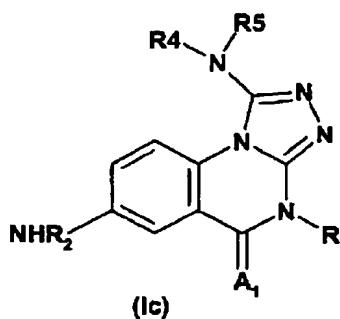


in which  $A_1$ , R,  $R_4$  and  $R_5$  are as defined above and  $P_1$  is a protecting group,

15 to conditions allowing the removal of the protecting group, in order to obtain a compound of general formula I.

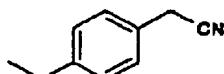
When  $X_1$  is H and  $X_2$  is  $NR_2R_x$  in which  $R_2$  is as defined above and  $R_x$  represents  $R_2$  or  $R_3$  as defined above, the compounds of formula I corresponding to this definition can also be

20 obtained in particular by reacting a compound of general formula Ic :

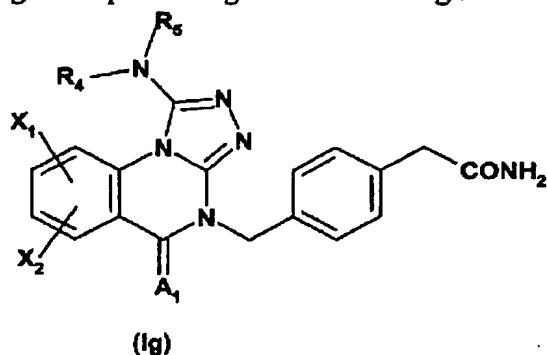


in which  $A_1$ ,  $R$ ,  $R_2$ ,  $R_4$  and  $R_5$  are as defined above,  
with a compound of formula  $R_x X_5$  in which  $R_x$  and  $X_5$  are as defined above, in order to  
5 obtain a compound of general formula I.

When  $R$  is

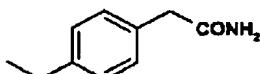


10 the compounds of formula I corresponding to this definition can also be obtained in particular by dehydrating a compound of general formula Ig :

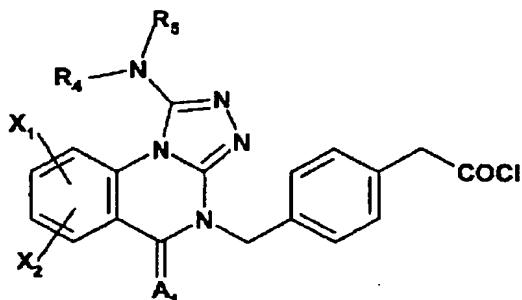


15 in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above,  
in order to obtain a compound of general formula I.

When  $R$  is



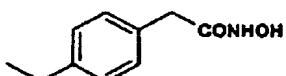
20 the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If:



(If)

in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above,  
with aqueous ammonia in order to obtain a compound of general formula I.

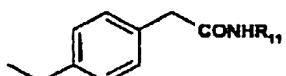
5 When R is



the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with hydroxylamine in order to obtain a compound of general formula I.

10

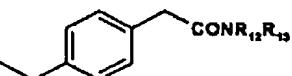
When R is



the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with the compound of formula

15  $R_{11}NH_2$  in which  $R_{11}$  has the same meaning as  $R_2$ , in order to obtain a compound of general formula I.

When R is



20 the compounds of formula I corresponding to this definition can also be obtained in particular by reacting a compound of general formula If with the compound of formula  $HNR_{12}R_{13}$  in which  $R_{12}$  and  $R_{13}$  have the same meaning as  $R_4$  and  $R_5$ , respectively, in order to obtain a compound of general formula I.

25 The invention also relates to a pharmaceutical composition comprising a compound of formula I or II and a pharmaceutically acceptable excipient.

The invention also relates to the use of a compound of formula I or II for the preparation of a medicinal product intended for the treatment of a disease or complaint which falls within the domain of a therapy by inhibition of phosphodiesterases, and more particularly of PDE4.

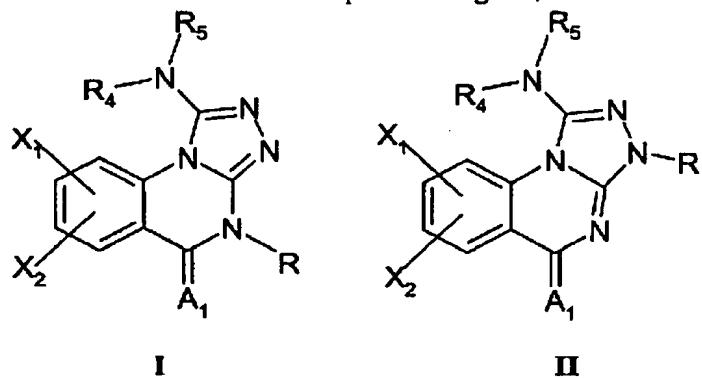
5

The invention also relates to a method for treating a disease or complaint which falls within the domain of therapy by inhibition of phosphodiesterases, and more particularly of PDE4, the said method comprising the administration to a patient of an effective concentration of a compound of formula I or II.

10

### **Detailed description of the invention**

The present invention thus relates to the compounds of general formula I or II:



15 in which  $X_1, X_2, A_1, R, R_4$  and  $R_5$  are as defined above.

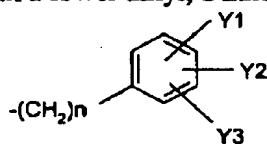
The invention relates particularly to the compounds of general formula I or II, in which:

$A_1$  represents an oxygen atom;

20  $X_1$  represents a hydrogen atom and  $X_2$  is a halogen, amino, lower alkyl, hydroxyl or  $-NHR_1$  group,  $R_1$  being as defined above:

R represents :

- a lower alkyl, lower alkenyl, arylalkynyl or 2-, 3- or 4-pyridylalkyl group optionally substituted on the pyridine ring with a lower alkyl, a halogen or a hydroxyl;

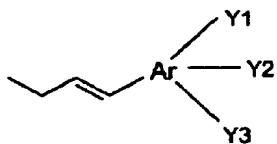


in which:

-  $n$  is an integer from 1 to 3,

5        - Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy,  
- Y<sub>1</sub> and Y<sub>2</sub> each represent a hydrogen atom and Y<sub>3</sub> represents a lower alkoxy group, an amino, nitro or hydroxyl group, a group -(CH<sub>2</sub>)<sub>s</sub>CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, a group (CH<sub>2</sub>)<sub>s</sub>-CN in which s, Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub> are as defined above, or a lower alkyl group optionally substituted with one or more halogen atoms, the position particularly preferred for the substituent Y<sub>3</sub> being position 4, or  
- Y<sub>1</sub> represents a hydrogen atom and Y<sub>2</sub> and Y<sub>3</sub>, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or

10



in which :

15        - Ar is as defined above ;  
- Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> each represent a hydrogen atom, or  
- Y<sub>1</sub> and Y<sub>2</sub> each represent a hydrogen atom and Y<sub>3</sub> is lower alkoxy or halogen ;

R<sub>4</sub> and R<sub>5</sub> represent :

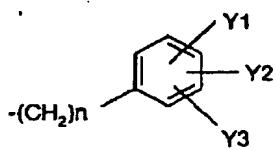
20        - lower alkyl when R<sub>4</sub> and R<sub>5</sub> are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R<sub>4</sub> and R<sub>5</sub> are different,  
- lower alkyl, it being possible for R<sub>4</sub> and R<sub>5</sub> to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

25        The invention relates more particularly to the compounds of general formula I in which :

X<sub>1</sub> represents a hydrogen atom,

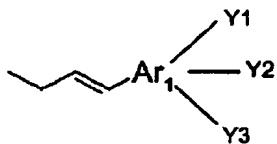
X<sub>2</sub> represents a halogen, amino, lower alkyl, hydroxyl or -NHR<sub>1</sub> group;

30        R represents :



in which :

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3,4,5-trimethoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy, amino, nitro or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms, a group  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  in which s is 0 or 1,  $Q_1$  is O, -NH- or a valency bond,  $Q_2$  is  $-(CH_2)_q-$ , q being equal to 0, 1, 2, 3 or 4 and  $Q_3$  is H, OH or  $-NX_3X_4$  in which  $X_3$  and  $X_4$  are as defined above, a group  $(CH_2)_s-CN$  in which s is 0 or 1, the position particularly preferred for the substituent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or



in which :

- $Ar_1$  is an aromatic ring comprising 6 atoms which can include a nitrogen atom in position 2, 3 or 4 and preferably in position 3 ;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when  $Ar_1$  does not comprise a nitrogen atom; and

$R_4$  and  $R_5$ , represent :

- lower alkyl when  $R_4$  and  $R_5$  are identical, aralkyl, cycloalkyl or cycloalkylalkyl when  $R_4$  and  $R_5$  are different,
- lower alkyl, it being possible for  $R_4$  and  $R_5$  to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or  $CO-Q_1-Q_2-Q_3$ , it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from

phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

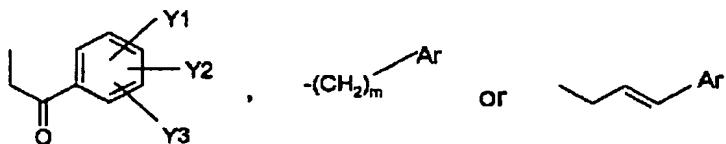
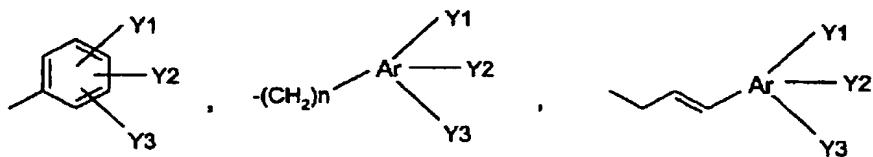
The invention also relates to compounds of general formula I or II in which :

5

$X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined in the summary of the invention ; and

$R$  represents :

10 - lower alkynyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl optionally substituted with a lower alkyl, a lower alkoxy, a hydroxyl group or a halogen,



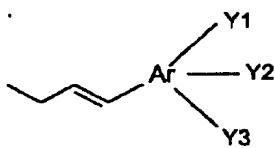
in which :

15 - n is an integer from 1 to 5 and m is an integer from 3 to 5 ;  
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N ;  
- Y1, Y2 and Y3, which may be identical or different, represent :  
- hydroxyl, mercapto, amino, nitro, halogen, -(CH<sub>2</sub>)<sub>s</sub>CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, (CH<sub>2</sub>)<sub>s</sub>-CN,  
20 in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

In another of its embodiments, the present invention relates to compounds of general formula I or II, in which :

25  $X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  are as defined in the summary of the invention ; and

$R$  represents :



in which :

- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N (the aromatic rings comprising 6 atoms, optionally including a nitrogen atom in position 2, 3 or 4, preferably in position 3, being particularly preferred);
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen, cyano,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

5

Preferably :

- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen.

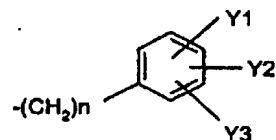
10

In another of its embodiments, the present invention relates to compounds of general formula I or II, in which :

X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined in the summary of the invention ; and

15

R represents :



in which :

20

- n is an integer from 1 to 3 ;
- Y1, Y2 and Y3, which may be identical or different, represent :
  - hydroxyl, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$  in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

25

Preferably :

- n is an integer from 1 to 3,

5. - Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> each represent a lower alkoxy group, more particularly methoxy and in particular 3,4,5-trimethoxy,

- Y<sub>1</sub> and Y<sub>2</sub> each represent a hydrogen atom and Y<sub>3</sub> represents a lower alkoxy, cyano, amino, nitro or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms or a group -(CH<sub>2</sub>)<sub>s</sub>CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub> in which s is 0 or 1, Q<sub>1</sub> is O, -NH- or a valency bond, Q<sub>2</sub> is -(CH<sub>2</sub>)<sub>q</sub>-, q being equal to 0, 1, 2, 3 or 4 and Q<sub>3</sub> is H, OH or -NX<sub>3</sub>X<sub>4</sub> in which X<sub>3</sub> and X<sub>4</sub> are as defined above, the position particularly preferred for the substituent Y<sub>3</sub> being position 4, or

10 - Y<sub>1</sub> represents a hydrogen atom and Y<sub>2</sub> and Y<sub>3</sub>, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group.

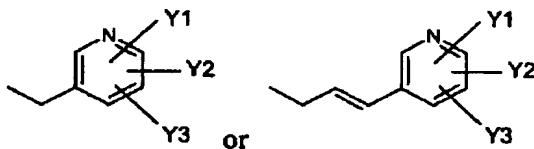
In another of its embodiments, the present invention relates to compounds of general formula I or II in which:

15

X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined in the summary of the invention; and

R represents :

20



in which :

25

- Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub>, which may be identical or different, represent :  
- hydrogen, hydroxyl, mercapto, amino, nitro, halogen, -(CH<sub>2</sub>)<sub>s</sub>CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, (CH<sub>2</sub>)<sub>s</sub>-CN, in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, optionally substituted with one or more halogen atoms.

30

Preferably :

- Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> each represent a hydrogen atom, or  
- Y<sub>1</sub> and Y<sub>2</sub> each represent a hydrogen atom and Y<sub>3</sub> is lower alkoxy or halogen.

In another of its embodiments, the present invention relates to compounds of general formula I or II in which :

X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R, R<sub>4</sub> and R<sub>5</sub> are as defined in the summary of the invention ; and :

35

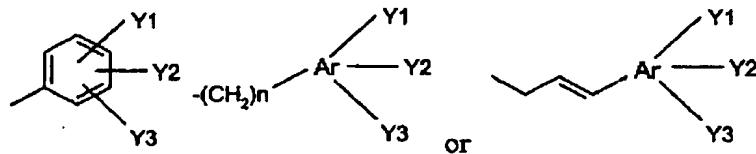
- when X<sub>1</sub> and X<sub>2</sub> represent hydrogen, R is not alkyl, phenyl, benzyl or allyl,

- when  $X_1$  represents hydrogen and  $X_2$  represents 7-Cl or  $CH_3$ , R is not an alkyl ; and
- when  $X_1$  represents hydrogen,  $X_2$  is not 8-Cl.

5 The invention also relates to a group of compounds of formula I or II which are particularly active as  $TNF\alpha$  inhibitors and in which :

- $A_1$  is O or S ;
- $X_1$  and  $X_2$ , which may be identical or different, represent :
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
- 10 - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, optionally substituted with one or more halogen atoms.
- Preferably,  $X_1$  is H and  $X_2$  is halogen, in particular 7-Br, or lower alkyl, in particular 7- $CH_3$ .
- R represents :

15



in which :

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N,
- 20 - Y1, Y2 and Y3, which may be identical or different, represent :
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$  in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, optionally substituted with one or more halogen atoms.

25

The substituents forming the group R which are particularly preferred include cinnamyl, 3-pyridylallyl, para-cyanobenzyl, dimethoxybenzyl and 3-pyridylmethyl.

30

35

- $R_4$  and  $R_5$ , which may be identical or different, represent : lower alkyl, it being possible for  $R_4$  and  $R_5$  to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or  $CO-Q_1-Q_2-Q_3$ . The substituents forming the group

NR<sub>4</sub>R<sub>5</sub> which are particularly preferred include dimethylamino, pyrrolidine and azepanyl.

The compounds which are particularly preferred as TNF $\alpha$  inhibitors include the following molecules :

- 3 7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 104 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 94 4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 98 7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 91 1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 103 1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Among the groups defined above, the following substituents are particularly preferred :

- In general, for the groups X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> :

- 10 - halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched containing from 1 to 6, and preferably from 1 to 3 carbon atoms,

- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
- lower alkylthio : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
- 5 - lower alkenyl : containing from 3 to 6 and preferably from 3 to 4 carbon atoms, more particularly allyl,
- lower alkynyl : containing from 3 to 9 carbon atoms, more particularly propargyl and phenylpropargyl,
- 2-, 3- or 4-pyridylalkyl in which the alkyl contains from 1 to 5 and preferably from 1 to 3 carbon atoms,
- 10 - aryl : containing from 5 to 8 and preferably 5 or 6 atoms,
- aralkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 4 carbon atoms,
- cycloalkyl : containing from 3 to 8 and preferably from 3 to 6 carbon atoms,
- 15 - cycloalkylalkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 3 carbon atoms and the cycloalkyl contains from 3 to 8 and preferably from 3 to 6 carbon atoms,
- lower alkyl, lower alkoxy or lower alkylthio optionally substituted with one or more halogen atoms: trisubstituted groups such as  $-(CH_2)_p-CF_3$ ,  $-O-(CH_2)_p-CF_3$  or  $-S-(CH_2)_p-CF_3$ , in which p is an integer from 0 to 3, will be preferred.
- 20

- In particular, for the groups  $X_1$  and  $X_2$  :
  - $-NH-R_1$ , or  $-NR_2R_3$  : when the lower alkyl is substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and  $CO-Q_1-Q_2-Q_3$ , the number of substituents ranges between 1 and 4, preferably between 1 and 2,
  - $-NR_2R_3$  : when  $R_2$  and  $R_3$  are linked to form a ring, this ring is characterized in that it preferably comprises :
    - between 1 and 4 and more particularly between 1 and 2 hetero atoms chosen from O, S and N, the cyclic substituents of this type preferably being saturated rings of the type  $C_mN$  in which m is an integer from 2 to 7, preferably from 4 to 6, the rings which are particularly preferred being chosen from the group comprising pyrrolidine, piperidine, homopiperidine or cyclooctylamine and
    - between 0 and 4, preferably between 0 and 2, more particularly between 1 and 2 substituents chosen from hydroxyl, keto, lower alkyl, lower alkoxy and  $-CO-Q_1-Q_2-Q_3$ ,
  - the groups  $X_1$  and  $X_2$  are particularly located in positions 7 and 8 of the aromatic ring of the compounds of formulae I and II to which they are linked.

- In particular, for the group R :

- the substituents Y1, Y2 and Y3 are particularly located in position 3 and/or 4 of the aromatic ring to which they are attached.

5 - Particularly, for the groups R<sub>4</sub> and R<sub>5</sub> :

- when R<sub>4</sub> and R<sub>5</sub> are linked to form a ring, this ring is characterized in that it preferably comprises :
  - between 1 and 4 hetero atoms chosen from O, S and N, the cyclic substituents of this type preferably being saturated rings of the type C<sub>m</sub>N, m being an integer from 2 to 7, the rings particularly preferred being chosen from the group comprising pyrrolidine, piperidine, homopiperidine and cyclooctylamine, and
  - between 0 and 4 and preferably between 0 and 2 substituents chosen from hydroxyl, keto, lower alkyl, lower alkoxy and -CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>.

10  
15

The following compounds are among the preferred compounds of the present invention :

- 1 -1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 2 -1-(azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 3 -7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 4 -7-Bromo-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 5 -7-Bromo-3-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 6 -1-Azepan-1-yl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 7 -1-(azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 8 -1-(azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 9 -1-(azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 10 -1-(azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 11 1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 12 1-(azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 13 1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 14 1-(azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 15 1-(azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 16 1-(azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 17 1-(azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 18 1-(azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 19 1-(azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 21 1-(azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 23 1-(azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 24 1-(azepan-1-yl)-7-chloro-4-(2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 25 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 26 1-(azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 27 1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

28 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

29 1-(azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

30 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

31 7-Chloro-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

32 1-(azepan-1-yl)-7-bromo-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

33 1-Azepan-1-yl-7-bromo-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

36 1-(azepan-1-yl)-7-bromo-4-(3-pyridinylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

38 1-Azepan-1-yl-7-bromo-4-[3-(4-chlorophenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

39 1-Azepan-1-yl-7-bromo-4-[3-(4-methoxyphenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

41 1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

42 7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

43 7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

44 7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

45 3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

48 7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl ester

51 7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

53 4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

54 7-Bromo-4-(3,5-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

55 7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

56 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

58 7-Bromo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chlorophenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxyphenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

63 7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

64 7-Bromo-4-(3,5-dimethylisoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

65 7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

66 7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

67 7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoroethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

68 7-Bromo-4-(2-hydroxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

69 7-Bromo-4-(2-diethylaminoethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

70 7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

71 7-Bromo-4-(2-phenoxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

72 7-Bromo-4-(2-phenylsulphenylethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

73 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)phenylacetic acid methyl ester

74 4-(7-Bromo-5-oxo-1-piperid-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

75 7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

77 7-Bromo-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 Bromo-dimethylamino-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

82 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetonitrile

84 7-Bromo-1-dimethylamino-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

86 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

87 7-Bromo-1-dimethylamino-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

88 7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

90 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)phenylacetic acid methyl ester

91 1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

94 4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

95 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

97 7-Methyl-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

98 7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

99 [4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

100 7-Methyl-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

103 1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

104 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

105 1-Dimethylamino-7-methyl-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

106 1-(azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

107 4-(4-Cyanobenzyl)-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

108 7-Hydroxy-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

109 1-(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

110 3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

111 1-(azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

112 1-Azepan-1-yl-7-chloro-3-(4-methylbenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

113 1-(azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

114 1-(azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

115 1-(azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

116 1-(azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

117 1-(azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

118 1-(azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

119 1-(azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

120 1-(azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

121 1-(azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

122 1-(azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

123 1-(azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

124 1-(azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

125 1-(azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

126 1-(azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

127 1-(azepan-1-yl)-7-chloro-3-(2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

128 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

129 1-(azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

130 1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

131 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

132 1-(azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

133 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)acetyl]-2-methoxybenzoic acid methyl ester

134 1-(azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

135 1-(azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

136 4-(1-(azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzonitrile

137 1-(azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

138 [4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl]acetic acid

139 1-(azepan-1-yl)-7-bromo-3-(pyrid-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

140 1-Azepan-1-yl-7-bromo-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

141 7-Bromo-3-((E)-3-phenylallyl)-1-piperid-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

142 7-bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

143 7-bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

144 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzonitrile

145 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzoic acid methyl ester

146 7-Bromo-3-(4-methoxybenzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

147 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl ester

148 7-Bromo-1-dimethylamino-3-(4-hydroxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

149 3-(benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

150 7-bromo-3-(3,5-dimethoxybenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

151 7-bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

152 7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

153 7-bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

154 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)phenylacetic acid methyl ester

155 7-Bromo-1-dimethylamino-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

156 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)phenylacetic acid methyl ester

157 1-(azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

158 7-methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

159 1-(azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

160 1-Azepan-1-yl-8-methyl-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

161 7-hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

162 1,8-bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

163 1-(azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

165 4-Benzyl-7-bromo-1-(butyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

166 4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

167 7-chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

168 7-chloro-4-methyl-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

169 7-Chloro-4-methyl-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

170 7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-azabicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

171 1-(azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

172 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

173 4-benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

174 4-benzyl-7-chloro-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

175 1-(azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

176 1-(azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

177 1-(azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

178 4-benzyl-7-bromo-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

179 4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

180 4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

181 4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

182 4-Benzyl-7-bromo-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

183 4-Benzyl-7-bromo-1-(4-phenylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

184 4-Benzyl-1-(4-benzylpiperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

185 4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyrid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

186 4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

187 4-Benzyl-7-bromo-1-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

188 4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

191 4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

192 4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

193 4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

194 1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

195 1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

196 4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

197 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

198 1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

199 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

200 1-(azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

201 1-(azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

202 1-(azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

203 1-(azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

204 1-(azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

205 7-chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

206 7-chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

207 1-(azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

208 7-chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

209 7-chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

210 1-(4-benzylpiperid-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

211 7-chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

212 1-(azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

213 1-(azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

214 1-(azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

215 4-Benzyl-7-bromo-1-(ethylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

216 4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

217 4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

218 4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

219 4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

220 4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

221 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)acetamide

222 N-[5-Oxo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl]acetamide

223 7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

225 7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

226 4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

227 7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

228 4-(7-Amino-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

229 7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

235 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)methanesulphonamide

236 4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

237 4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

238 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methylacetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-hydroxyacetamide

244 4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

245 4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

246 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

247 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo[4,3-a]quinazolin-5-one

Among the compounds mentioned above, the following compounds are preferred :

- 1 1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 3 7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 11 1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 13 1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 32 1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 41 1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 42 7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 43 7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 44 7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile
- 47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

48 7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl ester

51 7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

75 7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetonitrile

85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

94 4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

98 7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

103 1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

104 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

138 [4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl]acetic acid

164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

186 4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

218 4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

223 7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

227 7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

229 7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methylacetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-hydroxyacetamide

246 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

Among the compounds mentioned above, the following compounds are particularly preferred :

3 7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

41 1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

42 7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

43 7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

81 4-(Bromo-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoic acid methyl ester

85 7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

94 4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

98 7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

223 7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

227 7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N-methyacetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-N,N-dimethylacetamide

246 1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula I or II. A review of the pharmaceutically acceptable salts will be found in J. Pharm. 5 Sci., 1977, 66, 1-19. However, the expression "pharmacologically acceptable salt of a compound of formula I or II containing a basic function" means the addition salts of the compounds of formula I or II which are formed from non-toxic inorganic or organic acids such as, for example, the hydrobromic, hydrochloric, sulphuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulphonic and 10 isethionic acid salts and the like. The various quaternary ammonium salts of derivatives I or II are also included in this category of compounds of the invention. Also, the expression "pharmacologically acceptable salt of a compound of formula I or II containing an acidic function" means the usual salts of the compounds of formula I or II which are formed from non-toxic inorganic or organic bases such as, for example, alkali metal and alkaline-earth 15 metal (sodium, potassium, magnesium and calcium) hydroxides, amines

(dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

As mentioned previously, the compounds of formulae I and II of the present invention are 5 inhibitors of the enzyme phosphodiesterase and particularly of the enzyme phosphodiesterase 4 (PDE4).

In this respect, their use is recommended in the treatment of conditions or complaints which fall within the domain of a treatment by inhibition of PDE4. By way of example, the 10 use of the compounds of the present invention may be recommended in the treatment of septicaemia, multiple organ failure syndrome, asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (or COPD), allergic rhinitis, atopic dermatitis, pulmonary hypertension, cardiac or pulmonary insufficiency, congestive cardiac 15 insufficiency, psoriasis, inflammatory conditions of the digestive system such as haemorrhagic rectocolitis and Crohn's disease, conditions associated with a high level of TNF- $\alpha$  such as acute respiratory distress syndrome in adults and acute pancreatitis, rheumatoid arthritis, osteoporosis, multiple sclerosis and depression.

The PDE4 inhibitors of the present invention can also be used for the treatment of acute 20 pulmonary attack, ischaemia-induced neuronal damage, diabetes and chronic lymphoid leukaemia, and to attenuate the development of phenomena of tolerance or dependency on morphine. The compounds of the invention can also contribute towards reducing the losses of behavioural memory as observed, for example, in patients suffering from Alzheimer's disease.

The use of the compounds of the present invention may also be envisaged in the field of 25 urology, more particularly in the treatment of complaints of the prostate such as benign hypertrophy of the prostate or for the prevention of premature labour, for example by inhibiting the onset of contractions before term, preferably by the action of a PDE4 inhibitor on the myometrium.

30 **Structure-activity analysis of the compounds of formulae I and II**

Without wishing to be bound by a definitive theory, the inventors are of the opinion that the structural parameters mentioned below can be considered in order to guide a person skilled in the art in the choice of the combination of substituents which, beyond the 35 preferred compounds described in the present application, may allow not only an optimization of the inhibitory activity of PDE4, but also better optimization of important additional parameters such as the solubility, the bioavailability and the toxicity of the compounds envisaged.

Firstly, the inventors are of the opinion that the catalytic site of the enzyme PDE4 is large enough to accommodate overall a fairly wide range of structural changes in the substituents of the compounds of the invention which may be linked to this site. In this regard, the 5 inventors consider that the compounds of the present invention probably have the capacity of interacting with at least three separate points of the catalytic site of the isoenzyme PDE4. A first point of interaction is thought to be the aromatic ring comprising the substituents  $X_1$  and  $X_2$ . A second point of interaction is quite probably the substituent R while the third point of interaction is probably the group  $NR_4R_5$ . The potential functionality of each of 10 these binding points is proposed below.

However, it is important to point out here that the points of interaction listed above are not necessarily given in increasing or decreasing order of importance as regards their effect on the inhibitory activity of the compounds of the invention. In fact, it appears possible that 15 each of these points of interaction participates differently in the overall pharmacological properties of these compounds.

The first point of interaction listed above is thought to be the aromatic nucleus comprising the substituents  $X_1$  and  $X_2$ . This aromatic nucleus is thought to participate in the binding 20 of the compounds of the invention to the catalytic site of the enzyme PDE4, and it appears to be possible to modulate this binding by the choice of the substituents  $X_1$  and  $X_2$ .

The experiments carried out hitherto by the inventors tend to show that the substituents  $X_1$  and  $X_2$  currently preferred are those for which  $X_1$  is hydrogen and  $X_2$  is chosen from 25 halogen, more particularly Br and Cl, methyl, hydroxyl, amino and alkylamino. It is thus observed that among the preferred substituents of  $X_2$ , both electron-donating groups (e.g. methyl) and electron-withdrawing groups (e.g. Br, Cl) are found. It thus appears unlikely that  $X_2$  can be chosen solely as a function of the electronic properties of the recommended substituent. The inventors are of the opinion that the important selection criteria firstly 30 concern the position of the substituent on the aromatic nucleus, and then certain parameters such as the steric bulk of the substituent or the presence of a proton-donating or proton-accepting atom.

However, it appears to be accepted that the position of the substituents  $X_1$  and  $X_2$  on the 35 aromatic nucleus can have an influence on the final activity of the compounds of the invention. By way of example, compounds comprising a substituent other than hydrogen in position 7 are generally more active than the same compounds comprising this substituent in position 8. It thus appears probable that the choice and position of the substituents  $X_1$

and  $X_2$  makes it possible to shift the aromatic nucleus inside a cavity of the catalytic site of PDE4 and consequently modulate the inhibitory activity of the compounds of the invention. Furthermore, it appears that the compounds comprising a substituent in position 7 are more selective for the subtype PDE4 with respect to the other isoenzymes PDE5, 5 PDE3 and PDE1 than compounds comprising a substituent in position 8. The latter compounds have PDE4-inhibiting activity (although weaker), but they appear to be less selective with respect to the other isoenzymes. However, it also appears clear that although  $X_1$  and  $X_2$  can be chosen from a considerable number of substituents, better tolerance as regards this choice will be obtained if the substituent R is well targeted.

10

The second point of interaction of the compounds of the present invention with the enzyme PDE4 is thought to be substituent R. The inventors believe that it is quite probably the most important point of attachment of the molecule to the enzyme. In fact, it appears likely that this second point of interaction is in a vast cavity inside the catalytic site of PDE4. It is thus of fundamental importance for the substituent R to be able to attach to the catalytic site. However, the choice of groups included in the definition of R given above appears to demonstrate a certain flexibility as regards the attachment of R to this second binding site. In other words, it would appear to be possible to obtain inhibitory activity of PDE4 with compounds possessing substituents R that are structurally quite different. By way of 20 example, it will be preferred to use a substituent comprising an aromatic nucleus, which is itself preferably substituted, and separated from the main heterocycle by a chain comprising between 1 and 4 atoms, in particular carbon atoms, the said substituent having a relatively variable orientation in space. This observation appears to open the way to the possibility of more subtly modulating the overall properties of the compounds of the 25 invention.

The inventors are in fact of the opinion that although the substituent R quite probably remains a deciding factor in the PDE4-inhibiting activity of the compounds of the invention, it is probably possible to vary it and thus to act on important additional 30 pharmacological parameters without substantially impairing this inhibitory activity. By way of example, compounds respectively comprising a  $-\text{CH}_2\text{CH} = \text{CH-C}_6\text{H}_5$  or a substituted benzyl group, preferably substituted in position 4 (the other substituents being identical for the two compounds), in the substituent R have a PDE4-inhibiting activity of the same order of magnitude.

35

The third site of interaction of the compounds of the invention with PDE4 is quite probably the group  $-\text{NR}_4\text{R}_5$ . The inventors are of the opinion that this is probably a much more specific binding site than the two sites described above, although the displacement of the

substituent R in the enzymatic cavity can, however, have an influence on the specificity of this third site. The compounds of the invention having the best inhibitory activities are those for which R<sub>4</sub> and R<sub>5</sub>, which each represent a lower alkyl, are linked to form a ring, preferably a ring containing between 5 and 8 carbon atoms, more particularly a ring 5 containing 5 or 7 carbon atoms. The margin for manoeuvre of a person skilled in the art as regards the variation of this groups thus appears to be more limited.

In summary, the experiments carried out by the inventors with the compounds of the present invention appear to show that the size of the catalytic site of PDE4 is large enough 10 to accommodate several structural changes in the three binding sites described above. However, the greatest margin for manoeuvre nonetheless appears to be in the variation of the substituent R.

15 **Pharmaceutical formulation of the compounds of the invention**

The compounds of the invention are administered in the form of compositions that are suitable for the nature and seriousness of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product which can be absorbed in one or more 20 intakes. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula I) and 40% to 99.5% by weight of pharmaceutically suitable vehicle.

The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration. For example, the following pharmaceutical forms 25 may be envisaged, although the list given below is not limiting :

1) **Forms for oral administration :**

Drinkable solutions, suspensions, sachets of powder for drinkable solution, sachets of powder for drinkable suspension, gel capsules, gastro-resistant gel capsules, sustained-release forms, 30 emulsions, HPMR wafer capsules or gel capsules, lyophilizates to be melted under the tongue.

2) **Forms for parenteral administration :**

**Intravenous route :**

35 Aqueous solutions, water/co-solvent solutions, solutions using one or more solubilizing agents, colloidal suspensions, emulsions, nanoparticulate suspensions which can be used for the injection of sustained-release forms, dispersed forms and liposomes

Subcutaneous/intramuscular route :

In addition to the forms which can be used intravenously and which can also be used for the subcutaneous and intramuscular routes, other types of form such as suspensions, dispersed forms, sustained-release gels and sustained-release implants, can also be used.

5

3) Forms for topical administration :

Among the topical forms most commonly used are creams, gels (aqueous phases gelled with polymers), patches, which are dressings to be stuck directly on the skin and which can be used to treat dermatitides without percutaneous penetration of the active substance, 10 sprays, emulsions and solutions.

10

4) Forms for pulmonary administration :

Included in this category are forms such as solutions for aerosols, powders for inhalers and other appropriate forms.

15

5) Forms for nasal administration :

This especially concerns solutions for nose drops.

6) Forms for rectal administration :

20 Mention will be made, *inter alia*, of suppositories and gels.

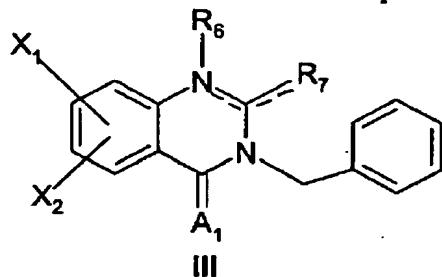
It may be envisaged to use forms allowing the administration of ophthalmic solutions or allowing the vaginal administration of the active principle.

25 Another important category of pharmaceutical form which can be used in the context of the present invention concerns forms for improving the solubility of the active principle. By way of example, it may be envisaged to use aqueous solutions of cyclodextrin, and more particularly forms comprising hydroxypropyl beta-cyclodextrin. A detailed review of this type of pharmaceutical form is presented in the article published under the reference *Journal of Pharmaceutical Sciences*, 1142-1169, 85 (11), 1996, and incorporated by way of reference in 30 the present application.

35 The various pharmaceutical forms recommended above are described in detail in the book «*Pharmacie galénique [Pharmaceutical pharmacy]*» by A. LEHIR (*published by Masson, 1992 (6<sup>th</sup> edition)*), which is incorporated by way of reference in the present application.

Intermediate compounds

The present invention also relates to the intermediate compounds of general formula III :



5

in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>6</sub> and R<sub>7</sub> are as defined above.

The invention relates particularly to the intermediate compounds of general formula III in which :

10

X<sub>1</sub> and X<sub>2</sub> are as defined above, and

R<sub>7</sub> is linked to the nitrogen at R<sub>6</sub> to form a triazole, substituted in position 1 with a Br, Cl, mercapto or lower thioalkyl, preferably CH<sub>3</sub>-S, group.

15 The following substituents are particularly preferred among the groups defined above :

- In general, for the groups X<sub>1</sub>, X<sub>2</sub>, R<sub>6</sub> and R<sub>7</sub> :

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
- lower alkoxy : linear or branched comprising from 1 to 5 and preferably from 1 to 3 carbon atoms,
- lower thioalkyl : linear or branched comprising from 1 to 5 and preferably from 1 to 3 carbon atoms.

20

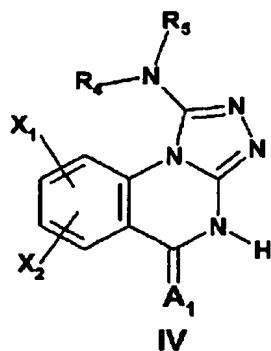
- In particular, for the groups X<sub>1</sub> and X<sub>2</sub> :

- X<sub>1</sub> and X<sub>2</sub> are particularly located in positions 6 and 7 of the main quinazolinone ring.

- In particular, for the groups R<sub>6</sub> and R<sub>7</sub> :

30 when R<sub>7</sub> is linked to the nitrogen at R<sub>6</sub> to form a ring, the ring formed is preferably a triazole, substituted in position 1 with a Br, Cl, mercapto or lower thioalkyl, preferably CH<sub>3</sub>-S-, group.

A second series of intermediates comprises compounds having the general formula IV below :



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above.

5

For the above groups, the following substituents are particularly preferred :

- In general, for the groups  $X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  :

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms ,
- lower alkyl, it being possible for  $R_4$  and  $R_5$  to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or  $CO-Q_1-Q_2-Q_3$ , it being possible for two of the atoms in the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl containing from 4 to 8 atoms including 1 to 4 hetero atoms.

10

15

20

- In particular, for the groups  $X_1$  and  $X_2$  :

$X_1$  and  $X_2$  are particularly located in positions 6 and 7 of the main quinazolinone ring.

25

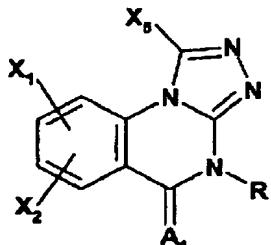
- In particular, for the groups  $R_4$  and  $R_5$  :

30

$R_4$  and  $R_5$  are lower alkyl, it being possible for  $R_4$  and  $R_5$  to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N, substituted with one or more groups chosen from hydroxyl, keto, lower alkyl and lower alkoxy. The substituents forming the

group  $NR_4R_5$  which are particularly preferred include pyrrolidine, 3-hydroxypyrrolidine, thiamorpholine, dimethylamino, azepanyl and piperidyl.

A third series of intermediates comprises compounds having the general formula V below :



(V)

in which  $X_1$ ,  $X_2$ ,  $X_5$ ,  $A_1$  and  $R$  are as defined above.

The following substituents are particularly preferred for the above groups :

- In general, for the groups  $X_1$ ,  $X_2$  et  $X_5$ :

10 - halogen : F, Cl, Br, I, preferably Br and Cl,  
- lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,  
- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms.

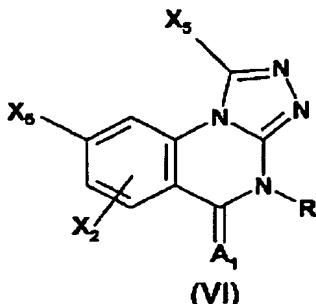
15

- In particular, for the groups  $X_1$  and  $X_2$  :

$X_1$  and  $X_2$  are particularly located in positions 6 and 7 of the main quinazolinone ring.

20 - In particular, for the group  $X_5$  :  $X_5$  is F, Br or Cl.

A fourth series of intermediates comprises compounds having the general formula VI below :



(VI)

25 in which  $X_2$ ,  $X_5$ ,  $A_1$  and  $R$  are as defined above.

The following substituents are particularly preferred for the above groups :

- In general, for the groups  $X_2$  and  $X_5$  :

5

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms.

- In particular, for the group  $X_2$  :

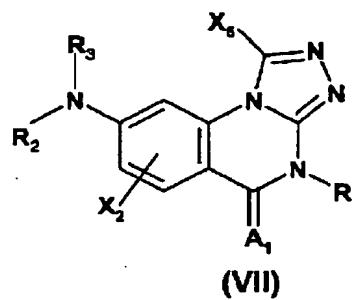
10

$X_2$  is particularly located in position 7 of the main quinazolinone ring.

- In particular, for the group  $X_5$  :  $X_5$  is F, Br or Cl.

15

A fifth series of intermediates comprises compounds having the general formula VII below :



in which  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R_2$  and  $R_3$  are as defined above.

The following substituents are particularly preferred for the above groups :

20

- In general, for the groups  $X_2$ ,  $X_5$ ,  $R_2$  and  $R_3$  :

25

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,
- lower alkoxy : linear or branched containing from 1 to 5 and preferably from 1 to 3 carbon atoms,
- hydrogen, lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$  groups, if being possible for  $R_2$  and  $R_3$  to be linked to form a ring comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and  $-CO-Q_1-Q_2-Q_3$ .

30

- In particular, for the group  $X_2$  :

$X_2$  is particularly located in position 7 of the main quinazolinone ring.

- In particular, for the group  $X_5$  :  $X_5$  is F, Br or Cl.

5

- In particular, for the groups  $R_2$  and  $R_3$  :

10  $R_2$  and  $R_3$ , which may be identical or different, are hydrogen or lower alkyl or  $R_2$  and  $R_3$  are linked to form a ring comprising one or more hetero atoms chosen from O, S and N and optionally substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and  $-CO-Q_1-Q_2-Q_3$ . Among the embodiments particularly preferred for the substituents  $NR_2R_3$  are azepanyl, pyrrolidine,  $NH_2$  and  $NHCH_3$  groups.

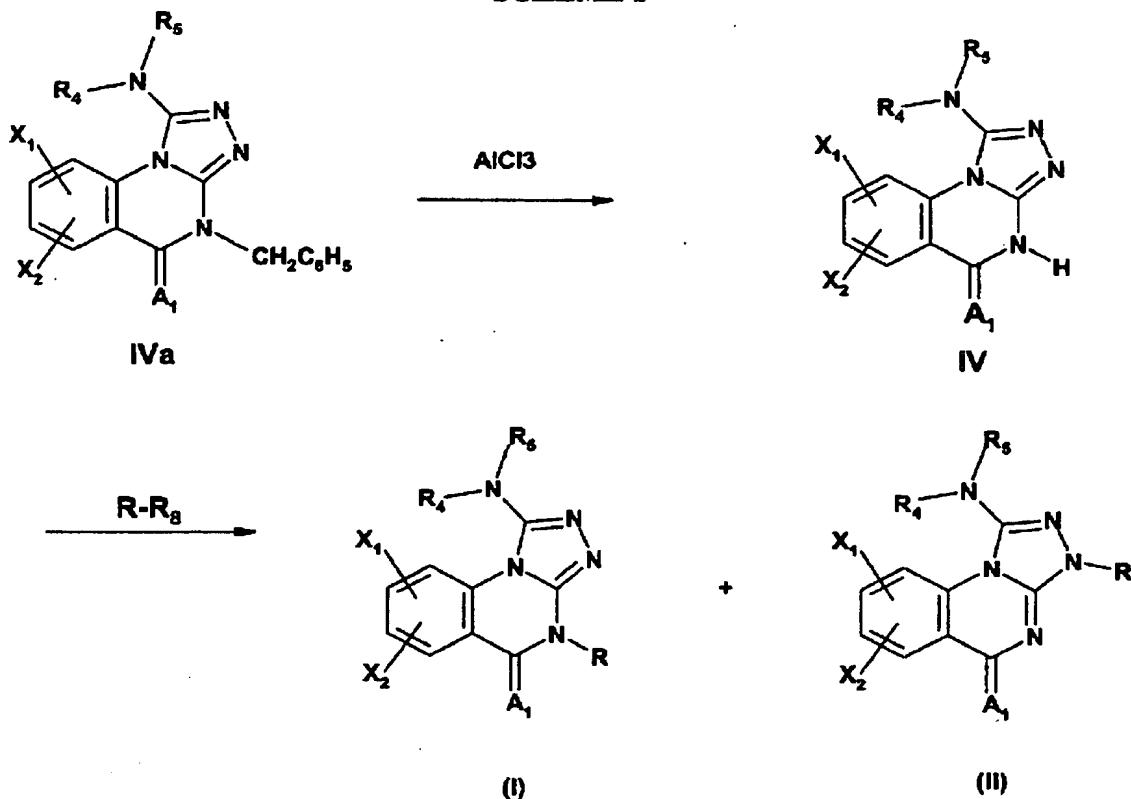
#### Processes for synthesizing the compounds of formulae I and II

15

A) The compounds of the present invention can be obtained by carrying out several synthetic processes. A number of these synthetic processes are described below.

20 The compounds of the present invention can firstly be obtained in a convergent manner by the method represented in Scheme 1.

SCHEME 1



in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R, R<sub>4</sub> and R<sub>5</sub> are as defined above and R<sub>8</sub> represents Cl, Br,  
 5 OSO<sub>2</sub>CH<sub>3</sub>, OSO<sub>2</sub>CF<sub>3</sub> or OSO<sub>2</sub>Ar.

4-Benzyl-1-aminotriazolo[4,3-a]quinazolin-5-one and/or -5-thione (IVa) is treated with aluminium trichloride in an aromatic solvent such as benzene or toluene to give the corresponding N-debenzylated compound (IV). This is then treated with a halide or a sulphonate chosen as a function of the desired substituent R under basic conditions ; for example sodium hydride in a solvent such as 1,2-dimethoxyethane (DME) or caesium carbonate in dimethylformamide, to give the 1-aminotriazolo[4,3-a]quinazolin-5-ones of formulae (I) and (II).

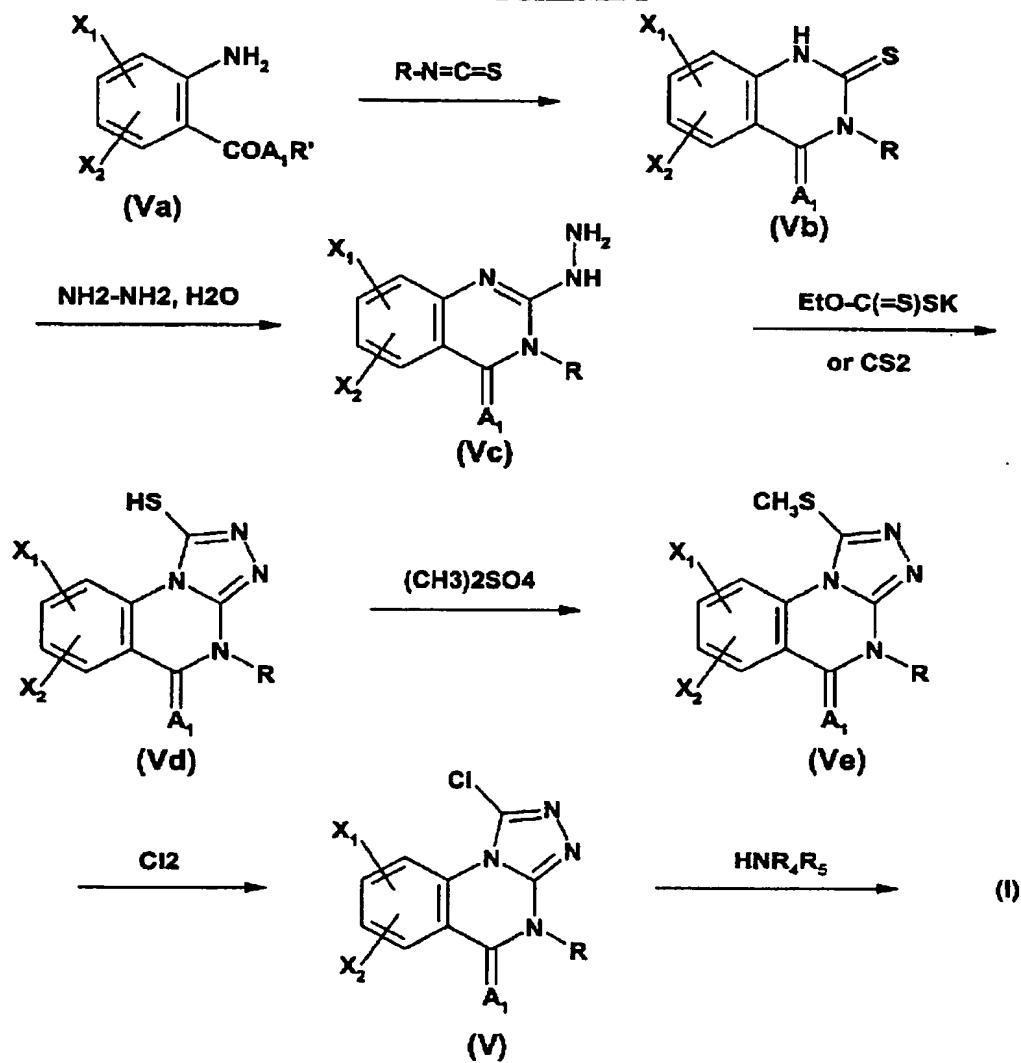
In fact, as a function of the basic conditions used, the alkylation is not particularly regioselective in certain cases. A mixture of N<sub>4</sub> and N<sub>3</sub> regioisomers, (I) and (II), respectively, is thus obtained.

The 2 compounds are generally separated by conventional chromatographic techniques.

B) Another example of a synthetic method used to construct the suitably substituted triazolo[4,3-a]quinazolin-5-one and/or -5-thione unit of formula (I) is illustrated in Scheme 2 :

5

SCHEME 2



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R$ ,  $R_4$ , and  $R_5$  are as defined above, and

$R$  represents a linear or branched lower alkyl group containing from 1 to 6 and preferably

10 from 1 to 3 carbon atoms.

An anthranilic acid or ester suitably substituted on the aromatic ring (Va) is first converted into the corresponding 2-thioquinazolin-4-one (Vb) and/or -4-thione by cyclization using an alkyl, aryl or aralkyl isothiocyanate, in a solvent such as acetic acid or pyridine.

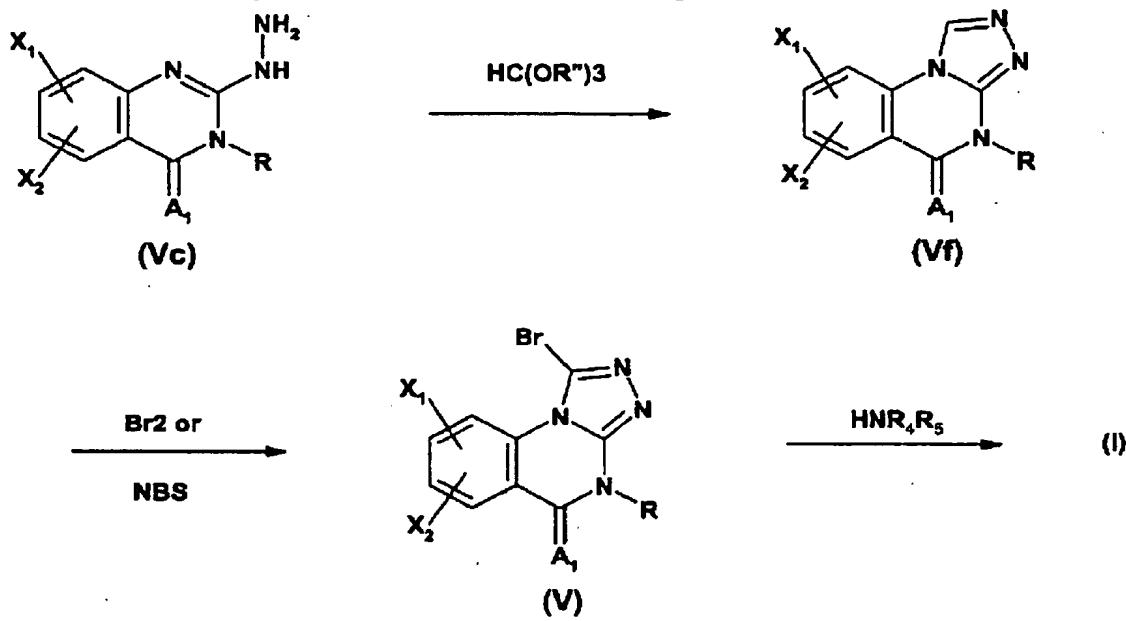
The thioquinazolin-4-one and/or -4-thione (Vb) is treated with hydrazine hydrate to give the 2-hydrazinoquinazolin-4-one and/or -4-thione (Vc) which is in turn cyclized into the 1-mercaptoptriazolo[4,3-a]quinazolin-5-one and/or -5-thione (Vd) by the action of potassium xanthogenate or other reagents such as CS<sub>2</sub>.

5 By the action of an alkylating agent such as dimethyl sulphate, the thiol (VI) is converted into the 1-methylthio derivative (Ve) which is then converted, by means of chlorine, into the 1-chlorotriazolo[4,3-a]quinazolin-5-one and/or -5-thione (V).

The latter compound is treated with a primary or secondary amine to finally give the 1-aminotriazolo[4,3-a]quinazolin-5-one of formula (I).

10

C) Another advantageous method in certain cases is represented in Scheme 3.



15 in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R, R<sub>4</sub> and R<sub>5</sub> are as defined above, and R'' represents a linear or branched lower alkyl containing from 1 to 6 and preferably from 1 to 3 carbon atoms, such as CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>.

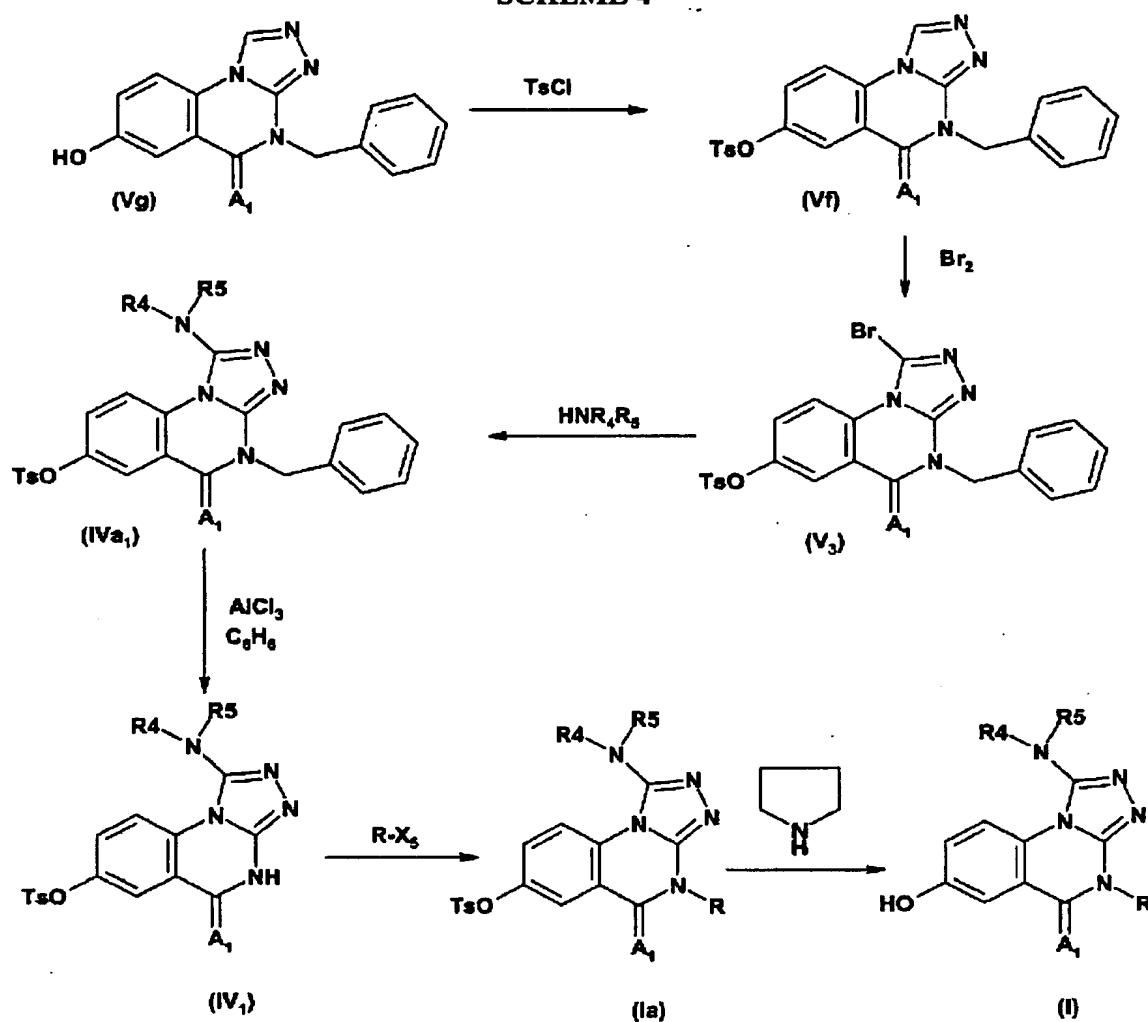
20 The 2-hydrazinoquinazolin-4-one and/or -4-thione (Vc), obtained from an anthranilate in 2 steps (as illustrated in Scheme 2), is cyclized by means of an alkyl orthoformate, in acidic medium, into the triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Vf). This is then brominated with bromine or N-bromosuccinimide (NBS) to give the 1-bromotriazolo[4,3-a]quinazolin-5-one and/or -5-thione (V).

This bromo derivative is finally treated with an ethanolic solution of a primary or secondary amine to give the 1-aminotriazolo[4,3-a]quinazolin-5-one and/or -5-thione of formula (I).

5 D) When  $X_1$  is H and  $X_2$  represents a reactive phenolic OH function, this group should generally be protected during the last steps in the synthesis of the compounds (I). By way of example, Scheme 4 shows the synthesis of such a compound hydroxylated in position 7. 4-Benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Vg), obtained by a method represented in Scheme 3, is treated with a compound allowing the 10 insertion of an oxygen-protecting group (P) onto the OH function. A person skilled in the art may select the appropriate protecting group without difficulty. The protecting group can be chosen, inter alia, from trimethylsilyl, methoxymethyl, tolylsulphonyl, methylsulphonyl (mesyl) and methoxyethoxymethyl (MEM). By way of example, the compound (Vg) is treated with tosyl chloride, in a solvent such as methylene chloride, in the presence of a 15 base or an amine such as triethylamine, to give the corresponding O-tosyl phenol (Vf). This compound is treated with bromine to give 4-benzyl-1-bromo-7-(4-tolylsulphonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (V<sub>3</sub>), which reacts with an amine HNR<sub>4</sub>R<sub>5</sub> at reflux, preferably in the presence of a base such as sodium bicarbonate, in a solvent such as dimethylformamide, to give 1-amino-4-benzyl-7-(4-tolylsulphonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (IVa<sub>1</sub>). 20

The benzyl group in position 4 can then be replaced with another group R, for example by debenzylating the compound (IVa<sub>1</sub>) obtained above by means of aluminium chloride in a solvent such as benzene, and then alkylating the intermediate obtained (IV<sub>1</sub>) by treatment 25 with a halide or a sulphonate R-X<sub>5</sub>, under basic conditions, to give the 1-amino-7-(4-tolylsulphonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Ia) which are variously substituted in position 4. These are preferably detosylated into the 7-hydroxy derivatives (I), for example by heating for a few hours in pyrrolidine.

SCHEME 4



in which  $\text{A}_1$ ,  $\text{R}_4$  and  $\text{R}_5$  are as defined above.

5

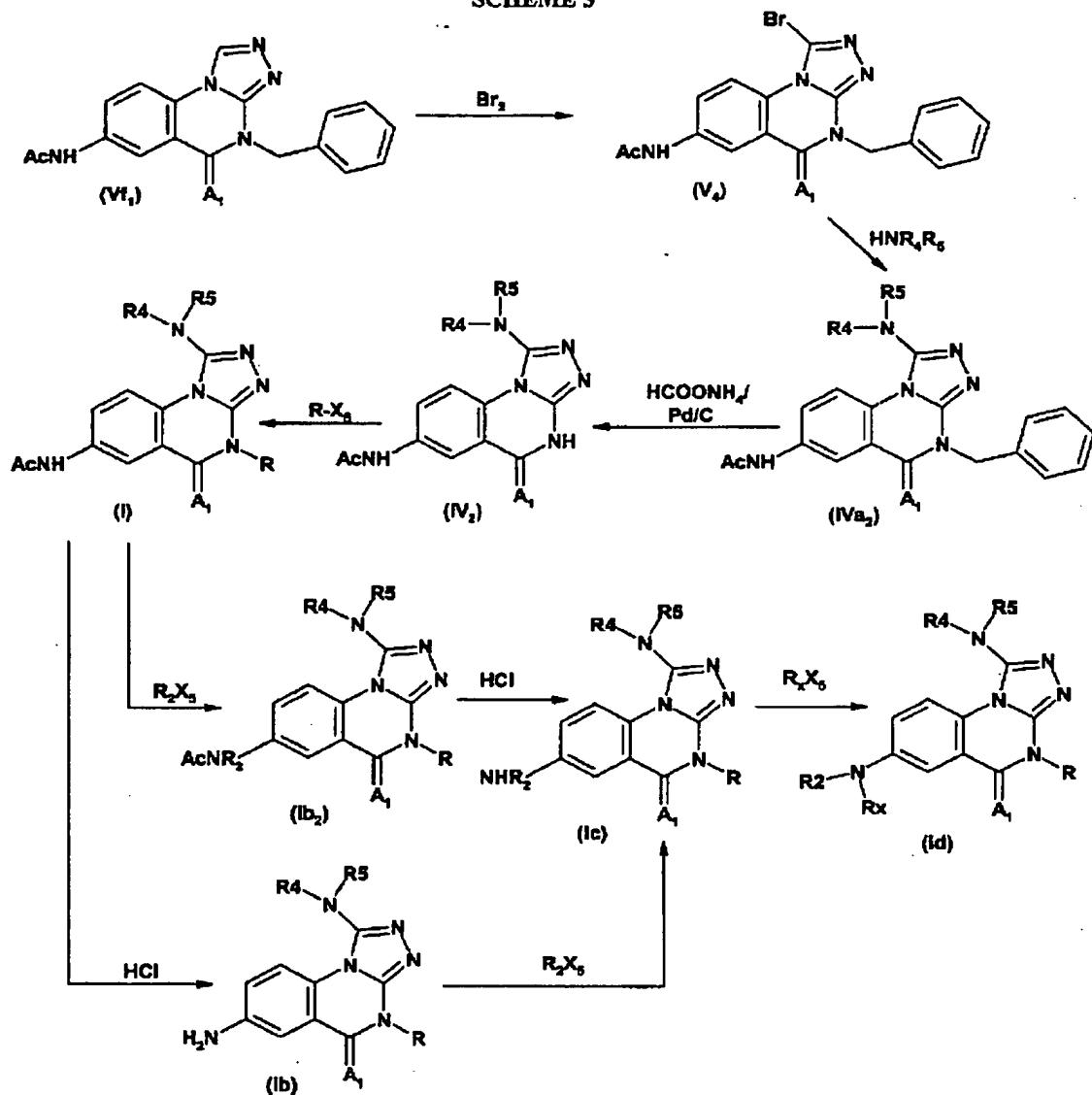
E) When  $\text{X}_1$  represents H and  $\text{X}_2$  represents a reactive anilino function :  $\text{NH}_2$ ,  $\text{NHR}_2$  or  $\text{NR}_2\text{R}_x$  ( $\text{R}_2$  as defined above and  $\text{R}_x$  represents  $\text{R}_2$  or  $\text{R}_3$  as defined above), the amino group  $\text{NH}_2$  should generally be protected during the last steps in the synthesis of the compounds (I). By way of example, Scheme 5 shows the synthesis of such a compound aminated in position 7. 7-Acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione ( $\text{Vf}_1$ ), obtained by a method represented in Scheme 3, is treated with bromine to give 7-acetamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione ( $\text{V}_4$ ). This compound is reacted with an amine  $\text{HNR}_4\text{R}_5$  at reflux, preferably in the presence of a base such as sodium bicarbonate, in a solvent such as dimethylformamide, to give 7-acetamido-1-amino-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-

thione (IVa<sub>2</sub>). In the example described above, the protecting group (P<sub>1</sub>) for the NH function is an acetyl group. However, a person skilled in the art can select another protecting group, for example methylsulphonyl, tolylsulphonyl or phthalimido.

5 In this case, the benzyl group in position 4 can be replaced with another group R, for example by debenzylating the compound (IVa<sub>2</sub>) obtained above, using ammonium formate and palladium-on-charcoal, in a solvent such as tetrahydrofuran, and then alkylating the intermediate obtained (IV<sub>2</sub>) by treatment with a halide or a sulphonate R-X<sub>5</sub>, under basic conditions, to give the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (I) variously substituted in position 4. These can be N-deacetylated into final compounds (Ib) bearing an NH<sub>2</sub> function in position 7, by conventional methods such as, for example, heating to reflux in an aqueous hydrochloric acid solution. These compounds can in turn be treated, depending on the case, with a reagent R<sub>2</sub>-X<sub>5</sub> (R<sub>2</sub> and X<sub>5</sub> having the meaning given above) to give an N-monosubstituted final compound (Ic), which

10 15 can itself then be treated with a reagent R<sub>x</sub>X<sub>5</sub> to give an N,N-disubstituted final compound (Id). It is also possible to treat the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (I) which are variously substituted in position 4, firstly with a reagent R<sub>2</sub>X<sub>5</sub> to give the compound (Ib<sub>2</sub>) which is then N-deacetylated to give the compound (Ic).

SCHEME 5

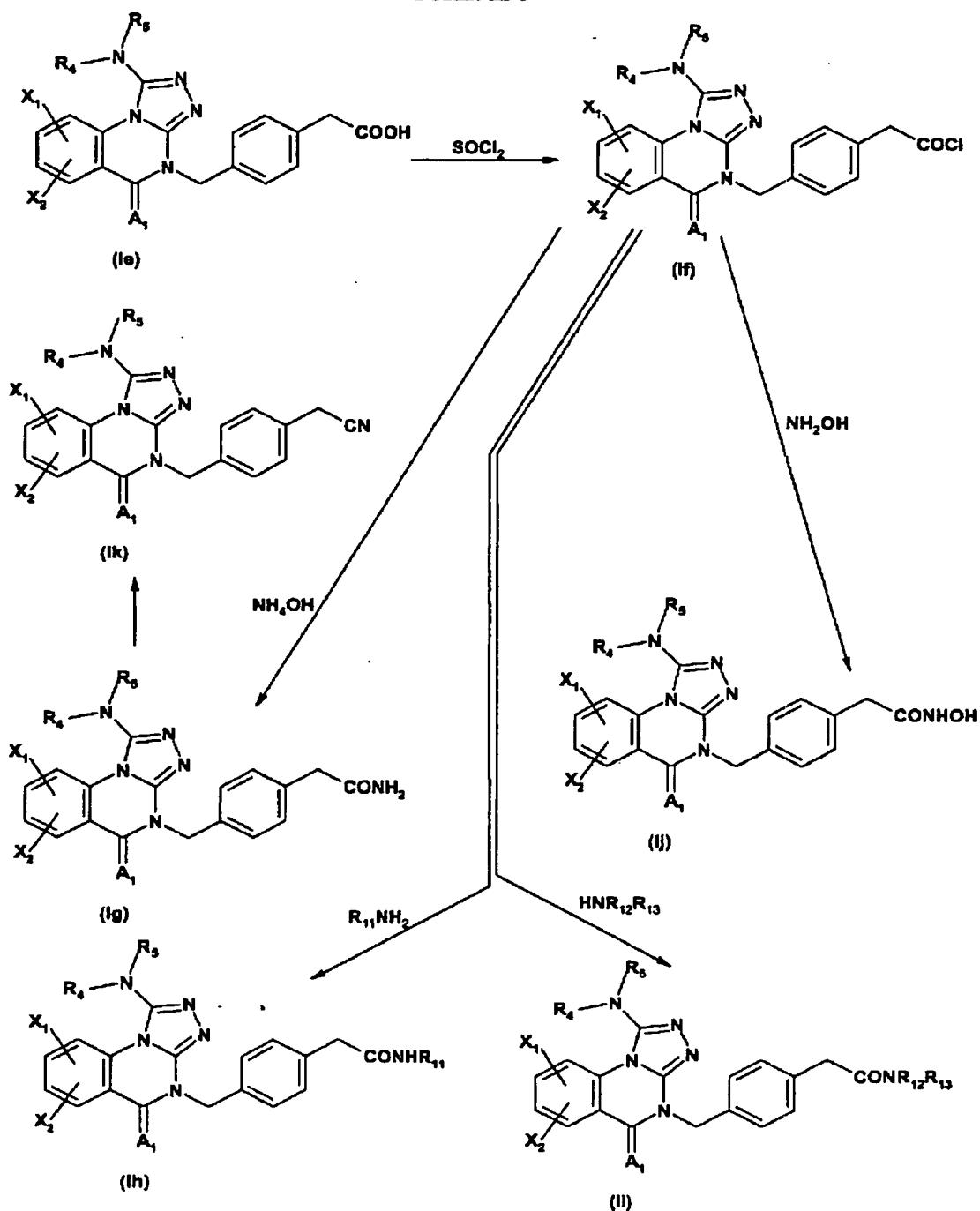


F) When the substituent R in position 4 of the compounds (I) represents a 4-(carboxymethyl)benzyl group, it may be advantageous to convert the carboxylic acid function into an ester, amide, nitrile or hydroxamic acid derivative. For this, the methods represented in Scheme 6 may be applied to an acid of general formula (Id). This is converted into an acid chloride (Ie) which is directly coupled either with aqueous ammonia to give a primary amide (If), or with a primary or secondary amine to give, respectively, a secondary amide (Ig) or tertiary amide (Ih) (in these structures, R<sub>11</sub> has the same meaning as R<sub>2</sub>, and R<sub>12</sub> and R<sub>13</sub> have the same meanings as R<sub>4</sub> and R<sub>5</sub>, respectively).

Hydroxamic acid (Ij) can be obtained by reacting the acid chloride (Ie) with hydroxylamine. The primary amide (If) can also be dehydrated by conventional methods that are known per se, such as, for example, using phosphorus pentoxide, to give the corresponding nitrile (Ik).

5

SCHEME 6

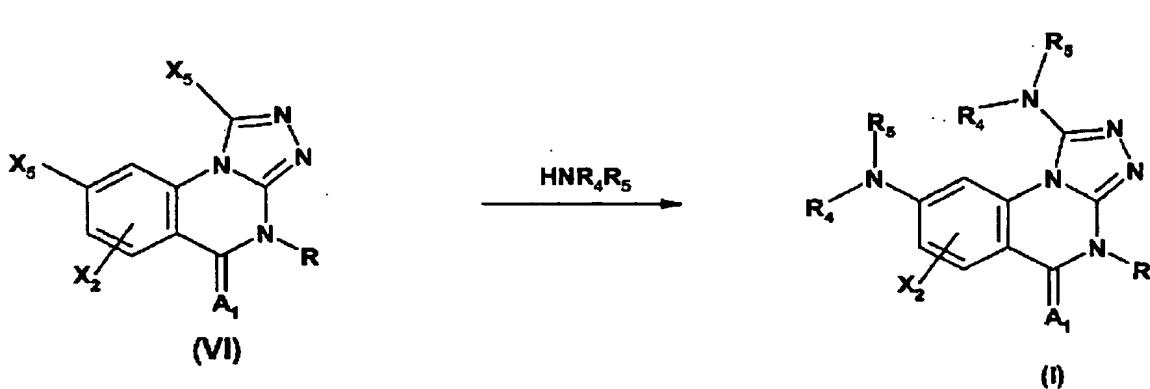


in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined above.

5 G) The compounds of structure (I) in which  $X_1$  or  $X_2$  represents an amino group  $NR_2R_3$  in position 8 which is identical to the group  $NR_4R_5$ , can also be obtained by heating the corresponding 1-bromo intermediate (VI;  $X_5$  = hal) in the presence of an excess of amine  $HNR_4R_5$ , without solvent or in a solvent such as dimethylformamide, as illustrated in Scheme 7.

SCHEME 7

10

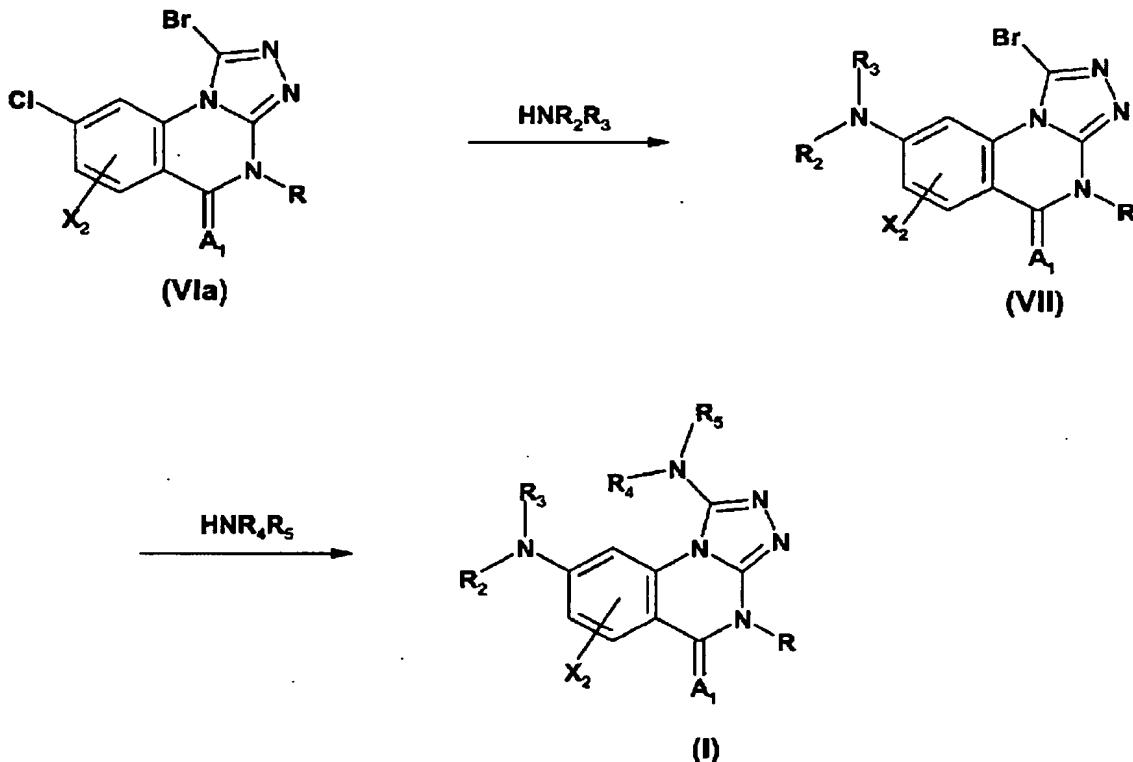


in which  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are as defined above.

15 H) However, it is preferable, for this type of reaction, to avoid substituents  $R$  comprising a halogen group which is liable to react competitively with the reagent  $HNR_4R_5$ .

H) When the 2 amino groups  $NR_2R_3$  and  $NR_4R_5$  are different, a slightly modified synthetic route is indicated in Scheme 8.

SCHEME 8



5 in which  $X_2$ ,  $A_1$ ,  $R$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are as defined above. The amino substituent  $NR_2R_3$  is in position 8.

A 1-bromo-8-chlorotriazolo[4,3-a]quinazolin-5-one and/or -5-thione (VIIa) suitably substituted at 4, and prepared as above by bromination of the derivative which is unsubstituted at 1, is treated with a light excess of amine  $HN R_2 R_3$ , in a solvent such as dimethylformamide, to give the intermediate (VII).  
10 This intermediate is in turn heated in an excess of amine  $HN R_4 R_5$ , in a solvent such as dimethylformamide, to give the compound (I).

15 Surprisingly, the inventors have found that the reactivity of the halogen atom in position 8 is much higher than the reactivity of the other halogen atom of the intermediate. This therefore allows a first selective reaction on this halogen in position 8, which can be followed by a reaction on the second halogen. The example above illustrates the use of chlorine in position 8. However, it is possible to use other halogens such as bromine and 20 fluorine, the latter proving to be particularly reactive.

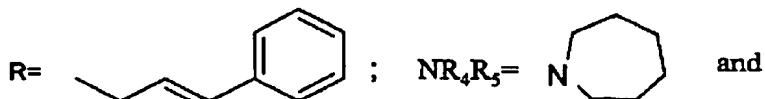
**Examples**

**A. Compounds of the type (I) and (II)**

**5 Examples 1 and 2**

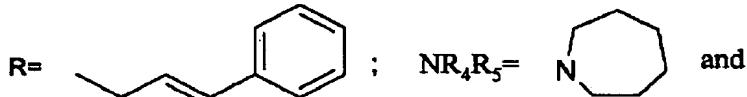
**METHOD A :** 1-Azepanyl-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 1)

(I):  $X_1 = 7 - \text{Cl}$  ;  $X_2 = \text{H}$  ;



10

1-Azepanyl-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 2)  
(II) :  $X_1 = 7 - \text{Cl}$  ;  $X_2 = \text{H}$  ;



15

2.5 g (7.87 mmol) of 1-azepanyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 35 ml of 1,2-dimethoxyethane are placed in a reactor protected from moisture, and then stirred.

20 240 mg of a 75% sodium hydride suspension (representing 7.90 mmol of NaH) are then added, under inert atmosphere.

The mixture is heated at 60°C with stirring for 6 hours.

1.56 g (7.90 mmol) of cinammyl bromide are then added portionwise.

The mixture obtained is then heated at 60°C for 20 hours with stirring.

25 After cooling, the suspension is poured into 200 ml of ice-cold water.

The mixture is extracted 3 times with ethyl acetate; the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the solvent is then evaporated off under vacuum.

3.5 g of a crude mixture of the 2 regioisomers is obtained (theory : 3.4 g).

30 The 2 isomers are separated by flash chromatography on a column of silica, eluting with a 99 methylene chloride / 1 methanol mixture.

The following are obtained, in order of elution :

1) 0.58 g of the compound of Example 1

Yield = 17%

m.p. (Tottoli) = 125°C

TLC (98 CH<sub>2</sub>Cl<sub>2</sub> / 2 CH<sub>3</sub>OH) = 0.60

<sup>1</sup> H NMR δ (ppm) CDCl<sub>3</sub> : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9

5 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H).

2) 2.1 g of the compound of Example 2

Yield = 61.5%

m.p. (Tottoli) = 188°C

TLC (98 CH<sub>2</sub>Cl<sub>2</sub> / 2 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.35.

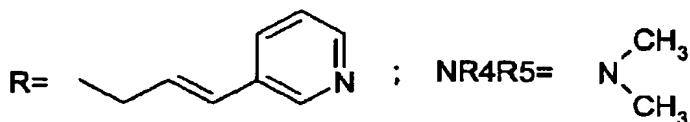
10 <sup>1</sup> H NMR δ (ppm) CDCl<sub>3</sub> :

1.7 – 2.0 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (dt, 1H) ; 6.75 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

**Example 3 :**

15 **METHOD B** : 7-Bromo-1-(N,N-dimethylamino)-4-[3-(3-pyridyl)allyl]-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one (Ex. 3)

(I): X<sub>1</sub> = 7 – Br ; X<sub>2</sub> = H ;



20 7.4 g (0.024 mol) of 7-bromo-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 200 ml of 1,2-dimethoxyethane are placed in a reactor equipped with a magnetic stirrer and a condenser, and are then stirred. 17.0g (0.052 mol) of caesium carbonate are added and the mixture is then stirred at room temperature for 15 minutes. 4.5 g (0.024 mol) of 3-(3-pyridyl)allyl chloride hydrochloride are then added portionwise, 25 after which the mixture is heated at 70°C with stirring for 3 hours. The solvent is evaporated off under vacuum and the residue is then suspended in 300 ml of ice-cold water. After repeated extractions with ethyl acetate, the combined organic phases are washed with saturated aqueous sodium chloride solution and dried over sodium sulphate, and the solvent is then evaporated off under vacuum.

30 The residue is chromatographed on a column of silica, eluting with a 98 CH<sub>2</sub>Cl<sub>2</sub>/2 CH<sub>3</sub>OH/0.2 NH<sub>4</sub>OH mixture. 6.3g of TLC-pure isomer (I) are recovered. This product is recrystallized from 20 ml of isopropanol to give 5.3 g of the compound of Example 3 :

Yield = 52%

35 <sup>1</sup> H NMR δ (ppm) CDCl<sub>3</sub> : 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.8 (d, 1H) ; 7.15 (m, 1H) ; 7.65 (d, 1H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.4 – 8.6 (m, 3H).

**Examples 4 and 5 :**

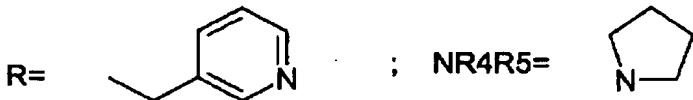
**METHOD C :** 7-Bromo-1-(pyrrolidin-1-yl)-4-[(3-pyridyl)methyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 4)

(I):  $X_1 = 7 - \text{Br}$  ;  $X_2 = \text{H}$  ;



7-Bromo-1-(pyrrolidin-1-yl)-3-[(3-pyridyl)methyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Ex. 5)

(II) :  $X_1 = 7 - \text{Br}$  ;  $X_2 = \text{H}$  ;



10 2.0g (0.006 mol) of 1-(pyrrolidin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 125 ml of dimethyl sulphoxide (DMSO) are placed in a reactor protected from moisture, equipped with a stirring system, followed by addition of 1.0g (0.018 mol) of finely ground potassium hydroxide. The mixture is stirred at room temperature for 1 h 30 min, until a slightly cloudy solution is obtained. 0.82 g (0.005 mol) of 3-picoly 15 chloride hydrochloride is then added in a single portion, after which stirring is continued at room temperature for 4 hours.

The mixture obtained is poured into ice-cold water and the resulting suspension is extracted three times with ethyl acetate. The combined organic extracts are washed with saturated NaCl solution and dried over  $\text{Na}_2\text{SO}_4$  and then concentrated under vacuum. 2.0 g 20 of a crude mixture of the 2 regioisomers are obtained, which are separated by chromatography on a column of silica, eluting with a 98  $\text{CH}_2\text{Cl}_2$ /2  $\text{CH}_3\text{OH}$ /0.4  $\text{NH}_4\text{OH}$  mixture.

The following are obtained, in the order of elution :

1) 1.2 g of the major product, which is recrystallized from methanol to give, after drying 25 under vacuum, 1.1 g of the compound of Example 4

**Yield = 57%**

**m.p. (Tottoli) = 206-207°C**

**TLC (97  $\text{CH}_2\text{Cl}_2$  / 3  $\text{CH}_3\text{OH}$  / 0.3  $\text{NH}_4\text{OH}$ ) :  $R_f = 0.30$**

1)  $^1\text{H NMR } \delta$  (ppm)  $\text{CDCl}_3$  : 1.95 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 30 7.3 (dd, 1H) ; 7.85 (d, 1H) ; 8.0 (d, 1H) ; 8.2 (d, 1H) ; 8.45 – 8.55 (m, 2H) ; 8.9 (s, 1H).

2) 0.25 g of the minor product, which is recrystallized from methanol to give, after drying under vacuum, 0.17 g of the compound of Example 5.

**Yield = 12%**

m.p. (Tottoli) = 261-262°C

TLC (97 CH<sub>2</sub>Cl<sub>2</sub> / 3 CH<sub>3</sub>OH / 0.3 NH<sub>4</sub>OH) : R<sub>f</sub> = 0.20

<sup>1</sup>H NMR δ (ppm) CDCl<sub>3</sub> : 1.9 – 2.05 (m, 4H) ; 3.2 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 7.2 (m, 1H) ; 7.7 (d, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.45 – 8.60 (m, 2H) ; 8.65 (s, 1H).

5

The compounds (I) of Examples 6 to 108 and the compounds (II) of Examples 109 to 162, in which X<sub>2</sub> = H<sub>1</sub>, are prepared according to the process of Example 1 :

Compounds (I) : Table 1

Compounds (II) : Table 2

10

TABLE 1

| Compound No. | X1   | R  | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|---|-----------|-----------|--------|
| 6            | H    | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>          |    | 11        | 144       | A      |
| 7            | 7-Cl | CH <sub>2</sub> =CHCH <sub>2</sub>                                 |    | 9         | -         | A      |
| 8            | 7-Cl | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>    |   | 16        | 163       | A      |
| 9            | 7-Cl | 2-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 6         | 160-162   | A      |
| 10           | 7-Cl | 3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 35        | 157       | A      |
| 11           | 7-Cl | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 20        | 166       | A      |
| 12           | 7-Cl | 4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 25        | 104-110   | A      |
| 13           | 7-Cl | 4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                   |  | 48        | 150       | A      |
| 14           | 7-Cl | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>    |  | 22        | 138       | A      |
| 15           | 7-Cl | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 49        | 165-168   | A      |
| 16           | 7-Cl | 2-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> |  | 6         | 98-100    | A      |
| 17           | 7-Cl | 3-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> |  | 22        | 138       | A      |
| 18           | 7-Cl | 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> |  | 26        | 138       | A      |

| Compound No. | X1   | R  | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|---|-----------|-----------|--------|
| 19           | 7-Cl | 3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>                  |    | 19        | -         | A      |
| 20           | 7-Cl | 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |    | 41        | 172       | A      |
| 21           | 7-Cl | (2-pyridyl)CH <sub>2</sub>   |    | 16        | 152       | A      |
| 22           | 7-Cl | (3-pyridyl)CH <sub>2</sub>   |    | 29        | 155       | A      |
| 23           | 7-Cl | (4-pyridyl)CH <sub>2</sub>   |    | 64        | 137       | A      |
| 24           | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>                      |    | 5         | 105       | A      |
| 25           | 7-Cl | 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> |    | 12        | 136       | A      |
| 26           | 7-Cl | C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub>                      |    | 17        | -         | A      |
| 27           | 7-Cl | C <sub>6</sub> H <sub>5</sub> C(=O)CH <sub>2</sub>                                 |  | 26.5      | 105-107   | A      |
| 28           | 7-Cl | 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> C(=O)                           |  | 30        | 191       | A      |
| 29           | 7-Cl | 4-ClC <sub>6</sub> H <sub>4</sub> C(=O)CH <sub>2</sub>                             |  | 36        | 190       | A      |
| 30           | 7-Cl | 4-(CH <sub>3</sub> O)-3-(COOCH <sub>3</sub> )-                                     |  | 18        | 140       | A      |
| 31           | 7-Cl | (3-pyridyl)-CH <sub>2</sub>  |  | 39        | 176       | C      |
| 32           | 7-Br | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |  | 8         | 179       | A      |
| 33           | 7-Br | 4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                   |  | 21        | 158       | A      |
| 34           | 7-Br | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |  | 21        | 190       | A      |
| 35           | 7-Br | 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |  | 23.5      | 185       | A      |
| 36           | 7-Br | (3-pyridyl)-CH <sub>2</sub>  |  | 4         | 180       | C      |

| Compound No. | X1   | R   | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|---|---|-----------|-----------|--------|
| 37           | 7-Br | (E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                |    | 64        | 155       | B      |
| 38           | 7-Br | (E) 4-Cl-C <sub>6</sub> H <sub>4</sub> CH=CHCH <sub>2</sub>           |    | 25        | 176       | B      |
| 39           | 7-Br | (E) 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH=CH          |    | 30        | 129       | B      |
| 40           | 7-Br | (E) (3-pyridyl)CH=CHCH <sub>2</sub>                                   |    | 12        | 185       | B      |
| 41           | 7-Br | (E) (4-pyridyl)CH=CHCH <sub>2</sub>                                   |    | 39        | 216       | B      |
| 42           | 7-Br | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>       |    | 53        | 215       | B      |
| 43           | 7-Br | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                     |    | 12        | 105       | A      |
| 44           | 7-Br | 4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                      |   | 42        | 166       | A      |
| 45           | 7-Br | 3-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                     |  | 52        | 206       | B      |
| 46           | 7-Br | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                     |  | 19        | 116       | A      |
| 47           | 7-Br | 4-(COOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH               |  | 54        | 205       | A      |
| 48           | 7-Br | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>       |  | 52        | 200       | B      |
| 49           | 7-Br | 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>    |  | 39        | 169       | B      |
| 50           | 7-Br | 4-(OCOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH               |  | 21        | 195       | B      |
| 51           | 7-Br | 4-OHC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                     |  | 13        | 288       | B      |
| 52           | 7-Br | 3,4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>  |  | 15        | 151       | A      |
| 53           | 7-Br | 3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |  | 21        | 194       | A      |
| 54           | 7-Br | 3,5-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>  |  | 31        | -         | A      |

| Compound No. | X1   | R  | NR4RS | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|-------|-----------|-----------|--------|
| 55           | 7-Br | 3,4,5-(CH <sub>3</sub> O)3C <sub>6</sub> H <sub>2</sub> CH <sub>2</sub>        |       | 35        | 141-143   | A      |
| 56           | 7-Br | 4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> C                        |       | 17        | 260       | B      |
| 57           | 7-Br | (E)C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                          |       | 57        | 152-155   | A      |
| 58           | 7-Br | (Z)C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                          |       | 24        | 110       | B      |
| 59           | 7-Br | (E) (4-ClC <sub>6</sub> H <sub>4</sub> )-CH=CHCH <sub>2</sub>                  |       | 45        | 187       | B      |
| 60           | 7-Br | (E) (4-CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH=CH                   |       | 32        | 171       | B      |
| 61           | 7-Br | (E) (3-pyridyl)-CH=CHCH <sub>2</sub>   |       | 10        | 102       | B      |
| 62           | 7-Br | (E) (4-pyridyl)-CH=CHCH <sub>2</sub>   |       | 38        | 167       | B      |
| 63           | 7-Br |  |       | 4         | 290(dec)  | B      |
| 64           | 7-Br |  |       | 60        | 221       | B      |
| 65           | 7-Br |  |       | 32        | 155       | B      |
| 66           | 7-Br | n-butyl  |       | 39        | 135       | B      |
| 67           | 7-Br | CH <sub>2</sub> CF <sub>3</sub>  |       | 14        | 202       | B      |
| 68           | 7-Br | CH <sub>2</sub> CH <sub>2</sub> OH   |       | 25        | 240       | B      |
| 69           | 7-Br | CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> |       | 50        | 215 (HCl) | C      |
| 70           | 7-Br |  |       | 36        | 204       | B      |
| 71           | 7-Br | CH <sub>2</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>                 |       | 25        | 171       | B      |
| 72           | 7-Br | CH <sub>2</sub> CH <sub>2</sub> SC <sub>6</sub> H <sub>5</sub>                 |       | 20        | 122       | B      |

| Compound No. | X1   | R  | NR4RS | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|-------|-----------|-----------|--------|
| 73           | 7-Br | CH(C <sub>6</sub> H <sub>5</sub> )COOCH <sub>3</sub>                               |       | 14        | 184       | B      |
| 74           | 7-Br | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |       | 72        | 200       | B      |
| 75           | 7-Br | 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |       | 67        | 178       | B      |
| 76           | 7-Br | (E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                             |       | 8         | -         | A      |
| 77           | 7-Br | (E) (3-pyridyl)CH=CHCH <sub>2</sub>  |       | 48        | 177       | B      |
| 78           | 7-Br | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                    |       | 56        | 223       | B      |
| 79           | 7-Br | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |       | 56        | 207       | B      |
| 80           | 7-Br | 4-OHC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |       | 15        | 284       | B      |
| 81           | 7-Br | 4-(COOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH                            |       | 35        | 197       | B      |
| 82           | 7-Br | 4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> C                            |       | 8         | 246       | B      |
| 83           | 7-Br | 4-(CH <sub>2</sub> CN)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                |       | <1        | 230       | B      |
| 84           | 7-Br | (3-pyridyl)-CH <sub>2</sub>  |       | 28        | 142       | B      |
| 85           | 7-Br | (E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                             |       | 63        | 171       | B      |
| 86           | 7-Br | (Z) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>                             |       | 28        | 167       | B      |
| 87           | 7-Br | (E) (4-pyridyl)-CH=CHCH <sub>2</sub>   |       | 48        | 115       | B      |
| 88           | 7-Br |  |       | <1        | 234       | B      |
| 89           | 7-Br | C <sub>6</sub> H <sub>5</sub> C=CCH <sub>2</sub>                                   |       | 15        | 159       | B      |
| 90           | 7-Br | CH(C <sub>6</sub> H <sub>5</sub> )COOCH <sub>3</sub>                               |       | 18        | 243       | B      |

| Compound No. | X1    | R                        | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|-------|--------------------------|---|-----------|-----------|--------|
| 91           | 7-CH3 | (3-pyridyl)-CH2          |    | 64        | 175       | C      |
| 92           | 7-CH3 | (E) C6H5CH=CHCH2         |    | 16        | 195       | A      |
| 93           | 7-CH3 | 4-CNC6H4CH2              |    | 84        | 166       | B      |
| 94           | 7-CH3 | 3,4-(CH3O)2C6H3CH2       |    | 52        | 184       | B      |
| 95           | 7-CH3 | 4-(COOCH3)C6H4CH         |    | 44        | 230       | B      |
| 96           | 7-CH3 | 4-(CH2COOH)C6H4C         |    | 21        | 262       | B      |
| 97           | 7-CH3 | (3-pyridyl)-CH2          |    | 10        | 139       | C      |
| 98           | 7-CH3 | (E) C6H5CH=CHCH2         |    | 17        | 173       | A      |
| 99           | 7-CH3 | 4-(CH2COOH)C6H4C         |  | 10        | -         | B      |
| 100          | 7-CH3 | (E) (3-pyridyl)CH=CHCH2  |  | 51        | 230       | B      |
| 101          | 7-CH3 | 4-CNC6H4CH2              |  | 73        | 201       | B      |
| 102          | 7-CH3 | 4-(CH2COOH)C6H4C         |  | 3         | -         | B      |
| 103          | 7-CH3 | (E) C6H5CH=CHCH2         |  | 50        | 171       | B      |
| 104          | 7-CH3 | (E) (3-pyridyl)CH=CHCH2  |  | 53        | 155       | B      |
| 105          | 7-CH3 | (E) (4-pyridyl)-CH=CHCH2 |  | 66        | 119       | B      |
| 106          | 8-CH3 | (E) C6H5CH=CHCH2         |  | 52        | -         | A      |
| 107          | 7-CN  | 4-CNC6H4CH2              |  | 43        | 147-149   | B      |
| 108          | 7-OH  | (E) C6H5CH=CHCH2         |  | 3         | 295(dec)  | A      |

- Compound 6 :

10  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.4 (m, 4H) ; 4.95 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.7 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.3 (t, 2H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- Compound 7 :

15  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.5 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.8 (d, 2H) ; 5.2 (d, 1H) ; 5.4 (d, 1H) ; 5.95 (m, 1H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 8 :

15  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.7 – 2.0 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 9 :

20  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.05 – 7.25 (m, 3H) ; 7.4 (d, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.45 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 10 :

25  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.6 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 2H) ; 7.55 (s, 1H) ; 7.65 (s, 1H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 11 :

30  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.65 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.55 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 12 :

35  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.4 (d, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent :  $\text{CDCl}_3$

5 - Compound 13 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.0 (m, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

5

10 - Compound 14 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ; 7.8 (d, 2H) ; 8.3 – 8.45 (m, 2H)

Solvent : CDCl<sub>3</sub>

10

15 - Compound 15 :

<sup>1</sup>H NMR δ (ppm) : 1.65 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.7 – 7.85 (m, 3H) ; 8.25 – 8.45 (m, 2H)

Solvent : CDCl<sub>3</sub>

15

20 - Compound 16 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (t, 1H) ; 6.9 (d, 1H) ; 7.1 (d, 1H) ; 7.2 (t, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

20

25 - Compound 17 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (m, 1H) ; 7.25 (m, 3H) ; 7.75 (d, 1H) ; 8.4 (m, 2H)

Solvent : CDCl<sub>3</sub>

25

30 - Compound 18 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.85 (d, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

30

35 - Compound 19 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.3 (d, 1H) ; 7.5 (d, 1H) ; 7.75 (m, 2H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent : CDCl<sub>3</sub>

35

35 - Compound 20 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.4 (s, 2H) ; 6.75 (d, 1H) ; 7.35 (m, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 21 :

5       $^1\text{H NMR } \delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.15 (m, 1H) ; 7.4 (d, 1H) ; 7.6 (m, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H) ; 8.45 (m, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 22 :

10      $^1\text{H NMR } \delta$  (ppm) : 1.6 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 1H) ; 7.7 (d, 1H) ; 8.0 (m, 1H) ; 8.3 (m, 2H) ; 8.5 (m, 1H) ; 8.9 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 23 :

15      $^1\text{H NMR } \delta$  (ppm) : 1.6 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.4 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H) ; 8.45 (d, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 24 :

20      $^1\text{H NMR } \delta$  (ppm) : 1.7 – 2.1 (m, 8H) ; 3.15 (t, 2H) ; 3.4 (m, 4H) ; 4.5 (t, 2H) ; 7.2-7.45 (m, 5H) ; 7.7 (d, 1H) ; 8.35 (s, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 25 :

25      $^1\text{H NMR } \delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.05 (t, 2H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 4.45 (t, 2H) ; 6.85 (d, 2H) ; 7.25 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 26 :

30      $^1\text{H NMR } \delta$  (ppm) : 1.7 – 2.0 (m, 8H) ; 2.2 (qn, 2H) ; 2.75 (t, 2H) ; 3.35 (m, 4H) ; 4.35 (t, 2H) ; 7.0 – 7.2 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 27 :

35      $^1\text{H NMR } \delta$  (ppm) : 1.65-1.85(m,8H) ; 3.35(m,4H) ; 5.7(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ; 8.05(d,1H) ; 8.15(m,3H) ; 8.4(d,1H)

Solvent : DMSO

5 - Compound 28 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.7 (s, 2H) ; 7.0 (d, 2H) ; 7.8 (d, 1H) ; 8.05 (d, 2H) ; 8.35 (s, 1H) ; 8.45 (d, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 29 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.7 (s, 2H) ; 7.45 (d, 2H) ; 7.8 (d, 1H) ; 8 (d, 2H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 30 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4 (s, 3H) ; 5.7 (s, 2H) ; 7.1 (d, 1H) ; 7.8 (d, 1H) ; 8.2 (d, 1H) ; 8.35 (s, 1H) ; 8.45 (s, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

20

- Compound 31 :

<sup>1</sup>H NMR δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1H) ; 8.55 (d, 1H) ; 8.9 (s, 1H)

Solvent : CDCl<sub>3</sub>

25

- Compound 32 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

30

- Compound 33 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.65 – 7.75 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

35

- Compound 34 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 3.35 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (dd, 2H) ; 7.8 (dd, 2H) ; 7.9 (m, 1H) ; 8.3 (dd, 1H) ; 8.5 (d, 1H)

Solvent : CHCl<sub>3</sub>

40

- Compound 35 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 36 :

5  $^1\text{H NMR } \delta$  (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (m, 1H) ; 7.9 (d, 1H) ; 8.1 (d, 1H) ; 8.35 (d, 1H) ; 8.5 (m, 2H) ; 8.95 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 37 :

10  $^1\text{H NMR } \delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 38 :

15  $^1\text{H NMR } \delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.35 – 6.45 (m, 1H) ; 6.75 – 6.85 (d, 1H) ; 7.2 – 7.35 (m, 4H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 39 :

20  $^1\text{H NMR } \delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.75 (s, 3H) ; 5.05 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.8 (m, 3H) ; 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 40 :

25  $^1\text{H NMR } \delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.35 (d, 1H) ; 8.45 (m, 1H) ; 8.5 (d, 1H) ; 8.6 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 41 :

30  $^1\text{H NMR } \delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.9 (m, 1H) ; 8.3 (d, 1H) ; 8.5 (m, 3H)

Solvent :  $\text{CDCl}_3$

- Compound 42 :

35  $^1\text{H NMR } \delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 43 :

5       $^1\text{H NMR } \delta \text{ (ppm)} : 1.9 - 2.05 \text{ (m, 4H)} ; 3.25 - 3.4 \text{ (m, 4H)} ; 5.35 \text{ (s, 2H)} ; 7.2 \text{ (d, 2H)} ; 7.6$   
      (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 44 :

10      $^1\text{H NMR } \delta \text{ (ppm)} : 2.0 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.45 \text{ (m, 4H)} ; 5.4 \text{ (s, 2H)} ; 6.9 - 7.0 \text{ (m,}$   
      2H) ; 7.6 - 7.7 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 45 :

15      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.15 \text{ (m, 4H)} ; 3.35 - 3.5 \text{ (m, 4H)} ; 5.45 \text{ (s, 2H)} ; 7.45 \text{ (t, 1H)} ; 7.55$   
      (d, 1H) ; 7.85 - 8.0 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 46 :

20      $^1\text{H NMR } \delta \text{ (ppm)} : 1.95 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.5 \text{ (m, 4H)} ; 5.45 \text{ (s, 2H)} ; 7.6 \text{ (d, 2H)} ; 7.8$   
      (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 47 :

25      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.45 \text{ (m, 4H)} ; 3.9 \text{ (s, 3H)} ; 5.5 \text{ (s, 2H)} ; 7.7 \text{ (d,}$   
      2H) ; 7.9 (d, 1H) ; 8.0 (d, 2H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 48 :

30      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.15 \text{ (m, 4H)} ; 3.3 - 3.45 \text{ (m, 4H)} ; 5.5 \text{ (s, 2H)} ; 7.75 - 7.9 \text{ (m, 3H)} ;$   
      8.1 - 8.2 (m, 3H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 49 :

35      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.15 \text{ (m, 4H)} ; 3.35 - 3.5 \text{ (m, 4H)} ; 3.75 \text{ (s, 3H)} ; 5.4 \text{ (s, 2H)} ; 6.8$   
      (d, 2H) ; 7.65 (d, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 50 :

5       $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.15 \text{ (m, 4H)} ; 2.25 \text{ (s, 3H)} ; 3.35 - 3.45 \text{ (m, 4H)} ; 5.45 \text{ (s, 2H)} ; 7.0$   
5      (d, 2H) ; 7.75 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 51 :

10      $^1\text{H NMR } \delta \text{ (ppm)} : 1.9 - 2.1 \text{ (m, 4H)} ; 3.2 - 3.45 \text{ (m, 4H)} ; 5.2 \text{ (s, 2H)} ; 6.7 \text{ (d, 2H)} ; 7.35$   
10     (d, 2H) ; 8 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H) ; 9.25 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 52 :

15      $^1\text{H NMR } \delta \text{ (ppm)} : 2.0 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.45 \text{ (m, 4H)} ; 3.85 \text{ (s, 3H)} ; 3.9 \text{ (s, 3H)} ; 5.4$   
15     (s, 2H) ; 6.8 (d, 1H) ; 7.2 - 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 53 :

20      $^1\text{H NMR } \delta \text{ (ppm)} : 2.0 - 2.1 \text{ (m, 4H)} ; 3.3 - 3.4 \text{ (m, 4H)} ; 5.35 \text{ (s, 2H)} ; 5.9 \text{ (s, 2H)} ; 6.7 \text{ (d,}$   
20     1H) ; 7.15 - 7.3 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

Compound 54 :

25      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.4 \text{ (m, 4H)} ; 3.75 \text{ (s, 6H)} ; 5.4 \text{ (s, 2H)} ; 6.35 \text{ (s,}$   
25     1H) ; 6.8 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 55 :

30      $^1\text{H NMR } \delta \text{ (ppm)} : 2 - 2.1 \text{ (m, 4H)} ; 3.35 - 3.45 \text{ (m, 4H)} ; 3.8 \text{ (s, 3H)} ; 3.85 \text{ (s, 6H)} ; 5.4 \text{ (s,}$   
30     2H) ; 7 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 56 :

35      $^1\text{H NMR } \delta \text{ (ppm)} : 1.95 - 2.1 \text{ (m, 4H)} ; 3.25 - 3.45 \text{ (m, 4H)} ; 3.55 \text{ (s, 2H)} ; 5.4 \text{ (s, 2H)} ;$   
35     7.25 (d, 2H) ; 7.35 (d, 2H) ; 8.15 (d, 1H) ; 8.2 (d, 1H) ; 8.35 (s, 1H) ; 12.2 - 12.5 (m, 1H)

Solvent :  $\text{CDCl}_3$

5 - Compound 57 :

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.4 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 58 :

<sup>1</sup>H NMR δ (ppm) : 2.0 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.2 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 59 :

<sup>1</sup>H NMR δ (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5 (d, 2H) ; 6.4 (m, 1H) ; 6.85 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.85 (m, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

20

Solvent : CDCl<sub>3</sub>

25 - Compound 60 :

<sup>1</sup>H NMR δ (ppm) : 1.95 – 2.10 (m, 4H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 4.95 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.75 – 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.15 (m, 1H) ; 8.45 (m, 1H)

Solvent : CDCl<sub>3</sub>

30

- Compound 61 :

<sup>1</sup>H NMR δ (ppm) : 1.95 – 2.15 (m, 4H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (m, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.75 – 6.9 (d, 1H) ; 7.2 (m, 1H) ; 7.6 – 7.7 (m, 1H) ; 7.85 – 7.95 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)

Solvent : CDCl<sub>3</sub>

35

- Compound 62 :

<sup>1</sup>H NMR δ (ppm) : 1.9 – 2.05 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.25 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.45 – 8.55 (m, 3H)

Solvent : CDCl<sub>3</sub>

40

- Compound 63 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 1.9 (m, 2H) ; 3.25 (m, 2H) ; 5.1 (s, 2H) ; 6.9 (s, 1H) ; 7.4 (s, 1H) ; 8 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (s, 1H) ; 11.8 (m, 1H)

Solvent : DMSO

- Compound 64 :

5  $^1\text{H}$  NMR  $\delta$  (ppm) : 2.05 – 2.15 (m, 4H) ; 2.4 (s, 3H) ; 2.6 (s, 3H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 65 :

10  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.25 – 1.75 (m, 8H) ; 1.9 – 2.05 (m, 4H) ; 2.5 – 2.7 (m, 1H) ; 3.3 – 3.4 (m, 4H) ; 4.2 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 66 :

15  $^1\text{H}$  NMR  $\delta$  (ppm) : 1 (t, 3H) ; 1.4 – 1.55 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 – 3.5 (m, 4H) ; 4.3 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 67 :

20  $^1\text{H}$  NMR  $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.0 (q, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 68 :

25  $^1\text{H}$  NMR  $\delta$  (ppm) : 2 (m, 4H) ; 3.15 (m, 1H) ; 3.3 (m, 4H) ; 4.05 (m, 2H) ; 4.5 (m, 2H) ; 7.08 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 69 :

30  $^1\text{H}$  NMR  $\delta$  (ppm) : 1.1 (t, 6H) ; 2.0 – 2.1 (m, 4H) ; 2.65 (q, 4H) ; 2.9 (t, 2H) ; 3.35 – 3.45 (m, 4H) ; 4.4 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 70 :

35  $^1\text{H}$  NMR  $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 2.3 (s, 1H) ; 3.35 – 3.5 (m, 4H) ; 5.1 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 71 :

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.45 (m, 2H) ; 4.75 (m, 2H) ; 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 72 :

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.45 (m, 6H) ; 4.6 (m, 2H) ; 7.1 (m, 1H) ; 7.2 (m, 2H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 73 :

<sup>1</sup>H NMR δ (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.08 (s, 3H) ; 6.7 (s, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.7 – 7.85 (m, 3H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 74 :

<sup>1</sup>H NMR δ (ppm) : 1.4 – 1.6 (m, 1H) ; 1.7 - 2 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 5.5 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

20

- Compound 75 :

<sup>1</sup>H NMR δ (ppm) : 1.4 (m, 1H) ; 1.7 – 1.95 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.40 (s, 1H)

25 Solvent : CDCl<sub>3</sub>

- Compound 76 :

<sup>1</sup>H NMR δ (ppm) : 1.35 – 2.1 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (m, 2H) ; 5.1 (d, 2H) ; 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.1 – 7.5 (m, 5H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)

30 Solvent : CDCl<sub>3</sub>

- Compound 77 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.6 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.25 (m, 1H) ; 8.45 (m, 1H) ; 8.5

35 (m, 1H) ; 8.55 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 78 :

<sup>1</sup>H NMR δ (ppm) : 2.3 (s, 3H) ; 2.9 (s, 6H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 79 :

<sup>1</sup>H NMR δ (ppm) : 2.95 (s, 6H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 80 :

<sup>1</sup>H NMR δ (ppm) : 2.85 (s, 6H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.3 (d, 2H) ; 8 (d, 1H) ; 8.2 – 8.3 (m, 2H) ; 9.3 (s, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 81 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 3.9 (s, 3H) ; 5.45 (s, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 7.9 (m, 2H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

20

- Compound 82 :

<sup>1</sup>H NMR δ (ppm) : 2.85 (s, 6H) ; 3.6 (s, 2H) ; 5.35 (s, 2H) ; 7.25 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.3 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.45 (m, 1H)

Solvent : DMSO

25

- Compound 83 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.25 (m, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

30

- Compound 84 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 (m, 1H) ; 7.85 (m, 1H) ; 8.05 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 2H) ; 8.9 (s, 1H)

Solvent : CDCl<sub>3</sub>

35

- Compound 85 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.4 – 6.55 (dt, 1H) ; 6.9 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.55 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 86 :

5       $^1\text{H NMR } \delta \text{ (ppm)} : 2.95 \text{ (s, 6H)} ; 5.29 \text{ (d, 2H)} ; 5.7 - 5.8 \text{ (m, 1H)} ; 6.7 \text{ (d, 1H)} ; 7.2 - 7.45$   
          (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 87 :

10      $^1\text{H NMR } \delta \text{ (ppm)} : 2.9 \text{ (s, 6H)} ; 5.05 \text{ (d, 2H)} ; 6.55 - 6.7 \text{ (m, 1H)} ; 6.85 \text{ (d, 1H)} ; 7.2 \text{ (m,}$   
          2H) ; 7.85 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 3H)

Solvent :  $\text{CDCl}_3$

- Compound 88 :

15      $^1\text{H NMR } \delta \text{ (ppm)} : 2.8 \text{ (s, 6H)} ; 3.2 \text{ (s, 1H)} ; 4.9 \text{ (s, 2H)} ; 8.1 \text{ (m, 1H)} ; 8.2 \text{ (d, 1H)} ; 8.3 \text{ (s,}$   
          1H)

Solvent : DMSO

- Compound 89 :

20      $^1\text{H NMR } \delta \text{ (ppm)} : 2.9 \text{ (s, 6H)} ; 5.2 \text{ (s, 2H)} ; 7.2 \text{ (m, 3H)} ; 7.4 \text{ (m, 2H)} ; 7.85 \text{ (m, 1H)} ; 8.2$   
          (d, 1H) ; 8.55 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 90 :

25      $^1\text{H NMR } \delta \text{ (ppm)} : 2.95 \text{ (s, 6H)} ; 3.85 \text{ (s, 3H)} ; 6.8 \text{ (s, 1H)} ; 7.3 - 7.4 \text{ (m, 3H)} ; 7.75 - 7.9$   
          (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 91 :

30      $^1\text{H NMR } \delta \text{ (ppm)} : 1.75 - 1.9 \text{ (m, 8H)} ; 2.5 \text{ (s, 3H)} ; 3.4 - 3.5 \text{ (m, 4H)} ; 5.5 \text{ (s, 2H)} ; 7.2 -$   
          7.3 (dd, 1H) ; 7.6 - 7.65 (d, 1H) ; 8.05 - 8.01 (d, 1H) ; 8.2 (s, 1H) ; 8.3 - 8.35 (d, 1H) ;  
          8.55 (d, 1H) ; 8.95 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 92 :

35      $^1\text{H NMR } \delta \text{ (ppm)} : 1.75 - 2 \text{ (m, 8H)} ; 2.5 \text{ (s, 3H)} ; 3.4 - 3.5 \text{ (m, 4H)} ; 5.1 \text{ (d, 1H)} ; 5.4 -$   
          5.55 (dt, 1H) ; 6.9 - 7 (d, 1H) ; 7.2 - 7.3 (m, 4H) ; 7.4 (d, 2H) ; 7.6 (d, 1H) ; 8.2 (s, 1H) ;  
          8.3 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 93 :

5       $^1\text{H NMR } \delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (d, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 94 :

10      $^1\text{H NMR } \delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.3 – 7.4 (m, 2H) ; 7.5 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

15     - Compound 95 :

$^1\text{H NMR } \delta$  (ppm) : 2.1 – 2.2 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.6 (m, 1H) ; 7.7 (m, 2H) ; 7.95 – 8 (m, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

20     - Compound 96 :

$^1\text{H NMR } \delta$  (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 3.6 (s, 2H) ; 5.3 (s, 2H) ; 7.3 (m, 2H) ; 7.45 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (s, 1H) ; 8.2 (d, 2H) ; 12.4 (m, 1H)

Solvent : DMSO

25     - Compound 97 :

$^1\text{H NMR } \delta$  (ppm) : 1.95 (m, 4H) ; 2.5 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.35 (dd, 1H) ; 7.55 (d, 1H) ; 8.05 (s, 1H) ; 8.15 (d, 1H) ; 8.5 (d, 1H) ; 8.7 (s, 1H)

Solvent : DMSO

30     - Compound 98 :

$^1\text{H NMR } \delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.45 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.85 – 6.95 (d, 1H) ; 7.1 – 7.45 (m, 5H) ; 7.6 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

35     - Compound 99 :

$^1\text{H NMR } \delta$  (ppm) : 2.4 – 3.75 (m, 13H) ; 5.35 (s, 2H) ; 7.1 – 7.5 (m, 4H) ; 7.8 (d, 1H) ; 8.1 (s, 1H) ; 8.25 (d, 1H)

Solvent : DMSO

- Compound 100 :

5       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.5 (s, 3H) ; 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.65 (m, 2H) ; 5.1 (m, 2H) ;  
6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.2 (m, 2H) ; 8.45 (d,  
1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 101 :

10       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (m, 2H) ; 8.15  
- 8.25 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 102 :

15       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.2 (s, 3H) ; 2.6 (s, 6H) ; 3.25 (s, 2H) ; 5.1 (s, 2H) ; 7 (m, 2H) ; 7.15 (m,  
2H) ; 7.5 (m, 1H) ; 7.8 (s, 1H) ; 8 (d, 1H) ; 12 (m, 1H)

Solvent : DMSO

- Compound 103 :

20       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.5 (s, 3H) ; 3 (s, 6H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ;  
7.15 – 7.4 (m, 6H) ; 7.6 (d, 1H) ; 8.2 (m, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 104 :

25       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 – 6.55 (dt, 1H) ; 6.8 – 6.85  
(d, 1H) ; 7.2 (m, 1H) ; 7.6 (dd, 1H) ; 7.7 (dd, 1H) ; 8.2 – 8.25 (m, 2H) ; 8.4 (d, 1H) ; 8.6 (s,  
1H)

Solvent :  $\text{CDCl}_3$

- Compound 105 :

30       $^1\text{H}$  NMR  $\delta$  (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.6 – 6.7 (dt, 1H) ; 6.8 (d, 1H) ;  
7.2 (d, 2H) ; 7.6 (d, 1H) ; 8.2 – 8.25 (dd, 2H) ; 8.5 (d, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 106 :

35       $^1\text{H}$  NMR  $\delta$  (ppm) : 1.7 - 2 (m, 8H) ; 2.55 (m, 3H) ; 3.35 – 3.6 (m, 4H) ; 5.1 (d, 2H) ; 6.45  
(dt, 1H) ; 6.85 (d, 1H) ; 7.1 – 7.45 (m, 6H) ; 8.25 (m, 2H)

Solvent :  $\text{CDCl}_3$

- Compound 107 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (d, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 2H) ; 7.7 (m, 2H) ; 8.0 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 108 :

<sup>1</sup>H NMR δ (ppm) : 1.9 (m, 4H) ; 3.25 (m, 4H) ; 6.85 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.6 – 6.7 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.35 – 7.4 (d, 2H) ; 7.5 (s, 1H) ; 8.05 (d, 1H) ; 10.1 (m, 1H),

Solvent : DMSO

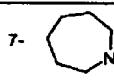
10

TABLE 2

| Compound No. | X1   | R  | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|---|-----------|-----------|--------|
| 109          | H    | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>          |    | 28        | 176       | A      |
| 110          | 7-Cl | CH <sub>2</sub> =CHCH <sub>2</sub>                                 |    | 24        | 173       | A      |
| 111          | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                      |  | 58        | 148       | A      |
| 112          | 7-Cl | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>    |  | 50        | 182       | A      |
| 113          | 7-Cl | 2-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 77        | 228       | A      |
| 114          | 7-Cl | 3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 31        | 166       | A      |
| 115          | 7-Cl | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 60        | 245       | A      |
| 116          | 7-Cl | 4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 38        | 244       | A      |
| 117          | 7-Cl | 4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                   |  | 42.5      | 224       | A      |
| 118          | 7-Cl | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>    |  | 39        | 232       | A      |
| 119          | 7-Cl | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                  |  | 46        | > 260     | A      |
| 120          | 7-Cl | 2-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> |  | 57        | 184       | A      |

| Compound No. | X1   | R  | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|--|---|-----------|-----------|--------|
| 121          | 7-Cl | 3-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                 |    | 46        | 163       | A      |
| 122          | 7-Cl | 4-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                 |    | 32.5      | 164-165   | A      |
| 123          | 7-Cl | 3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>                  |    | 60        | 212       | A      |
| 124          | 7-Cl | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |    | 39        | 153       | A      |
| 125          | 7-Cl | (2-pyridyl)CH <sub>2</sub>   |    | 9         | 153       | A      |
| 126          | 7-Cl | (3-pyridyl)CH <sub>2</sub>   |    | 8         | 184       | C      |
| 127          | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>                      |    | 7         | 196       | A      |
| 128          | 7-Cl | 4(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>  |   | 61        | 196       | A      |
| 129          | 7-Cl | C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub>                      |  | 36        | 130       | A      |
| 130          | 7-Cl | C <sub>6</sub> H <sub>5</sub> C(=O)CH <sub>2</sub>                                 |  | 38.5      | 230-232   | A      |
| 131          | 7-Cl | 4(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> C(=O)CH <sub>2</sub>             |  | 42        | 238       | A      |
| 132          | 7-Cl | 4-ClC <sub>6</sub> H <sub>4</sub> C(=O)CH <sub>2</sub>                             |  | 59        | 238       | A      |
| 133          | 7-Cl | 4(CH <sub>3</sub> O)-3-(COOCH <sub>3</sub> )                                       |  | 30        | 136       | A      |
| 134          | 7-Br | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |  | 57        | 247       | A      |
| 135          | 7-Br | 4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                   |  | 54        | 216       | A      |
| 136          | 7-Br | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                  |  | 53        | 293       | A      |
| 137          | 7-Br | 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> |  | 61        | 174       | A      |
| 138          | 7-Br | 4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> C                            |  | 1         | 269       | B      |

| Compound No. | X1   | R                    | NR4R5 | Yield (%) | m.p. (°C) | Method |
|--------------|------|----------------------|-------|-----------|-----------|--------|
| 139          | 7-Br | (3-pyridyl)CH2       |       | 4         | 192       | C      |
| 140          | 7-Br | (E) C6H5CH=CHCH2     |       | 70        | 198       | A      |
| 141          | 7-Br | (Z) C6H5CH=CHCH2     |       | 57        | 187       | A      |
| 142          | 7-Br | 4-ClC6H4CH2          |       | 18        | 185       | A      |
| 143          | 7-Br | 4-FC6H4CH2           |       | 16        | 233       | A      |
| 144          | 7-Br | 4-CNC6H4CH2          |       | 52        | 222       | A      |
| 145          | 7-Br | 4-(COOCH3)C6H4CH     |       | 31        | 193       | A      |
| 146          | 7-Br | 4-(CH3O)C6H4CH2      |       | 14        | 164       | B      |
| 147          | 7-Br | 4-(OCOCH3)C6H4CH     |       | 24        | 199       | B      |
| 148          | 7-Br | 4-OHC6H4CH2          |       | 15        | 283       | B      |
| 149          | 7-Br | 3,4-(OCH2O)C6H4CH2   |       | 57        | 234       | A      |
| 150          | 7-Br | 3,5-(CH3O)2C6H4CH2   |       | 21        | 168       | A      |
| 151          | 7-Br | 3,4,5-(CH3O)3C6H2CH2 |       | 21        | 199-201   | A      |
| 152          | 7-Br |                      |       | 4         | -         | B      |
| 153          | 7-Br | n-butyl              |       | 13        | 130       | B      |
| 154          | 7-Br | CH(C6H5)COOCH3       |       | 55        | 187       | A      |
| 155          | 7-Br | (E) C6H5CH=CHCH2     |       | 10        | 206       | B      |

| Compound No. | X1  | R   | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|---|---|---|-----------|-----------|--------|
| 156          | 7-Br  | CH(C <sub>6</sub> H <sub>5</sub> )COOCH <sub>3</sub>      |  | 32        | 83        | B      |
| 157          | 7-CH <sub>3</sub>   | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 43        | 193       | A      |
| 158          | 7-CH <sub>3</sub>   | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 35        | 225       | A      |
| 159          | 8-CH <sub>3</sub>   | CH <sub>3</sub>   |  | 70        | -         | A      |
| 160          | 8-CH <sub>3</sub>   | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 18        | -         | A      |
| 161          | 7-OH  | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 10        | 255       | A      |
| 162          |  | (E)<br>C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 28        | -         | A      |

Compound 109 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.85 (d, 2H) ; 6.35 – 6.45 (dt,

5 1H) ; 6.65 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.35 (t, 1H) ; 7.45 (d, 1H) ; 7.6 (t, 1H) ; 7.85 (t, 1H) ; 8.2 (d, 1H) ; 8.3 (d, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 110 :

10 <sup>1</sup>H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 4.8 (d, 2H) ; 5.25 – 5.4 (m, 2H) ; 5.9 – 6.1 (m, 1H) ; 7.55 – 8.4 (m, 3H)

Solvent : CDCl<sub>3</sub>

- Compound 111 :

15 <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.2 – 7.4 (m, 3H) ; 7.45 (d, 2H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 112 :

20 <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 8.45 (m, 7H)

Solvent : CDCl<sub>3</sub>

- Compound 113 :

5      <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.15 – 7.3 (m, 3H) ; 7.4 (d, 1H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 114 :

10     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.2 – 7.4 (m, 3H) ; 7.45 (s, 1H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 115 :

15     <sup>1</sup>H NMR δ (ppm) : 1.65 – 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.15 (s, 2H) ; 7.25 (d, 2H) ; 7.35 (d, 2H) ; 7.55 (d, 1H) ; 8.05 (d, 1H) ; 8.3 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 116 :

20     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (d, 2H) ; 7.35 (d, 2H) ; 7.45 (d, 2H) ; 7.6 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 117 :

25     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.35 (s, 2H) ; 7.5 – 7.7 (m, 5H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 118 :

30     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.5 – 7.7 (m, 5H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 119 :

35     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.35 (s, 2H) ; 6.9 (m, 2H) ; 7.2 (d, 1H) ; 7.3 (t, 1H) ; 7.6 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)  
Solvent : CDCl<sub>3</sub>

- Compound 120 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (m, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

5

- Compound 121 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 3.8 (s, 3H) ; 5.2 (s, 2H) ; 6.85 (d, 2H) ; 7.45 (d, 2H) ; 7.65 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 122 :

1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.3 (d, 1H) ; 7.4 (d, 1H) ; 7.5 (s, 1H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)

15

Solvent : CDCl<sub>3</sub>

- Compound 123 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.2 (s, 2H) ; 6.85 (d, 1H) ; 7.1 (m, 2H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

20

Solvent : CDCl<sub>3</sub>

- Compound 124 :

<sup>1</sup>H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 (m, 1H) ; 7.3 (d, 1H) ; 7.65 (m, 2H) ; 8.2 (d, 1H) ; 8.4 (s, 1H) ; 8.55 (d, 1H)

25

Solvent : CDCl<sub>3</sub>

- Compound 125 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.25 (m, 1H) ; 7.6 (d, 1H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H) ; 8.6 (d, 1H) ; 8.75 (s, 1H)

30

Solvent : CDCl<sub>3</sub>

- Compound 126 :

<sup>1</sup>H NMR δ (ppm) : 1.55 – 1.9 (m, 8H) ; 3.1 (t, 2H) ; 3.25 (m, 4H) ; 4.25 (t, 2H) ; 7.05 – 7.25 (m, 5H) ; 7.55 (d, 1H) ; 8.1 (d, 1H) ; 8.35 (s, 1H)

35

Solvent : CDCl<sub>3</sub>

- Compound 127 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.15 (t, 2H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 4.35 (t, 2H) ; 6.8 (d, 2H) ; 7.15 (d, 2H) ; 7.6 (d, 1H) ; 8.15 (d, 1H) ; 8.4 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 128 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 2.2 (m, 2H) ; 2.7 (t, 2H) ; 3.35 (m, 4H) ; 4.2 (t, 2H) ; 7 – 7.3 (m, 5H) ; 7.65 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 129 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.6 (s, 2H) ; 7.0 (d, 2H) ; 7.7 (d, 1H) ; 8 (d, 2H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 130 :

<sup>1</sup>H NMR δ (ppm) : 1.6-1.9(m,8H) ; 3.4(m,4H) ; 5.8(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ; 7.95(d,1H) ; 8.1(m,3H) ; 8.3(d,1H)

Solvent : DMSO

20

- Compound 131 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.55 (s, 2H) ; 7.45 (d, 2H) ; 7.65 (d, 1H) ; 7.9 (d, 2H) ; 8.2 (d, 1H) ; 8.4 (s, 1 H)

Solvent : CDCl<sub>3</sub>

25

- Compound 132 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 5.6 (s, 2H) ; 7.1 (d, 1H) ; 7.7 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (d, 1 H) ; 8.4 (m, 2H)

Solvent : CDCl<sub>3</sub>

30

- Compound 133 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 5.6 (s, 2H) ; 7.1 (m, 1H) ; 7.7 (m, 1H) ; 8.15 –8.45 (m, 4H)

Solvent : CDCl<sub>3</sub>

35

- Compound 134:

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.35 (m, 4H) ; 5.25 (s, 2H) ; 7.25 - 8.6 (m, 7 H)

Solvent : CDCl<sub>3</sub>

- Compound 135 :

5      <sup>1</sup>H NMR δ (ppm) : 1.65 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.25 (s, 2H) ; 6.95 – 7.1 (m, 2H) ; 7.4 – 7.55 (m, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 136 :

10      <sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.3 (s, 2H) ; 7.5 – 7.7 (m, 4H) ; 7.8 (m, 1H) ; 8.1 (dd, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 137 :

15      <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 3.25 – 3.4 (m, 4H) ; 3.8 (s, 3H) ; 3.82 (s, 3H) ; 5.2 (s, 2H) ; 6.8 (d, 1H) ; 7.05 – 7.1 (m, 2H) ; 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 138 :

20      <sup>1</sup>H NMR δ (ppm) : 1.6 – 1.85 (m, 8H) ; 3.2 - 3.4 (bs, 4H) ; 3.55 (s, 2H) ; 5.2 (s, 2H) ; 7.2 (m, 2H) ; 7.3 (m, 2H) ; 8 (m, 1H) ; 8.2 (m, 1H) ; 8.25 (s, 1H) ; 12.3 (bs, 1H)

Solvent : DMSO

- Compound 139 :

25      <sup>1</sup>H NMR δ (ppm) : 1.75 – 1.9 (m, 8H) ; 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.3 (m, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.1 (d, 1H) ; 8.65 (m, 2H) ; 8.8 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 140 :

30      <sup>1</sup>H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (m, 1H) ; 6.75 (d, 1H) ; 7.25 – 7.45 (m, 5H) ; 7.8 – 8.65 (m, 3H)

Solvent : CDCl<sub>3</sub>

- Compound 141 :

35      <sup>1</sup>H NMR δ (ppm) : 1.35 – 2.05 (m, 6H) ; 2.95 (t, 2H) ; 3.4 (d, 2H) ; 4.9 (d, 2H) ; 6.35 (dt, 1H) ; 6.75 (d, 1H) ; 7.25 – 7.45 (m, 5H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.65 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 142 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.25 (d, 2H) ; 7.4 (d, 2H) ; 7.75 (d, 1H) ; 7.95 (d, 1H) ; 8.55 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 143 :

<sup>1</sup>H NMR δ (ppm) : 1.95 – 2.1 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.2 (s, 2H) ; 6.95 – 7.1 (m, 2H) ; 7.35 – 7.5 (m, 2H) ; 7.75 (d, 1H) ; 7.95 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

- Compound 144 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.3 (s, 2H) ; 7.55 – 7.7 (m, 4H) ; 7.8 – 7.9 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

15

- Compound 145 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.3 (s, 2H) ; 7.5 (d, 2H) ; 7.8 (d, 1H) ; 7.9 – 8.05 (m, 3H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

20

- Compound 146 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.2 (s, 2H) ; 6.9 (d, 2H) ; 7.45 (d, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

25

- Compound 147 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.05 (d, 2H) ; 7.5 (d, 2H) ; 7.8 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

30

- Compound 148 :

<sup>1</sup>H NMR δ (ppm) : 2.7 (s, 6H) ; 5 (s, 2H) ; 6.6 (d, 2H) ; 7.1 (d, 2H) ; 7.9 (d, 1H) ; 8.0 (d, 1H) ; 8.1 (s, 1H) ; 9.35 (s, 1H)

Solvent : CDCl<sub>3</sub>

35

- Compound 149 :

<sup>1</sup>H NMR δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.15 (s, 2H) ; 5.9 (s, 2H) ; 6.75 (d, 1H) ; 6.9 – 7.0 (m, 2H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 150 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 3.75 (s, 6H) ; 5.2 (s, 1H) ; 6.65 (s, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.65 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 151 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.9 (s, 6H) ; 5.2 (s, 2H) ; 6.8 (s, 2H) ; 7.8 (d, 1H) ; 7.95 (d, 1H) ; 8.65 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 152 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2 (m, 4H) ; 3.35 (m, 4H) ; 5.2 (s, 2H) ; 7.15 (s, 1H) ; 7.6 (s, 1H) ; 8 – 8.15 (m, 2H) ; 8.3 (s, 1H) ; 12 (m, 1H)

Solvent : DMSO

- Compound 153 :

$^1\text{H NMR}$   $\delta$  (ppm) : 0.95 (t, 3H) ; 1.35 – 1.5 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 – 3.5 (m, 4H) ; 4.1 (t, 2H) ; 7.8 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 154 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2.45 – 2.55 (m, 4H) ; 3.25 – 3.4 (m, 4H) ; 3.7 (s, 3H) ; 6.6 (s, 1H) ; 7.35 – 7.50 (m, 3H) ; 7.55 (d, 2H) ; 8 – 8.1 (m, 2H) ; 8.3 (s, 1H)

Solvent : DMSO

- Compound 155 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2.9 (s, 6H) ; 4.8 (d, 2H) ; 6.2 – 6.3 (dt, 1H) ; 6.7 (d, 1H) ; 7.1 – 7.35 (m, 5H) ; 7.75 (d, 1H) ; 8.0 (d, 1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 156 :

$^1\text{H NMR}$   $\delta$  (ppm) : 2.9 (s, 6H) ; 3.8 (s, 3H) ; 6.6 (s, 1H) ; 7.35 – 7.45 (m, 3H) ; 7.55 (d, 2H) ; 7.8 (d, 1H) ; 8 (d, 1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 157 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 4.9 (d, 2H) ; 6.3 – 6.45 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.55 (d, 2H) ; 8.1 (d, 1H) ; 8.3 (s, 1H)

5 Solvent : CDCl<sub>3</sub>

- Compound 158 :

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.3 – 6.45 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.5 (m, 1H) ; 8 (d, 1H) ; 8.3 (d, 1H)

10 Solvent : CDCl<sub>3</sub>

- Compound 159 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.9 (m, 8H) ; 2.45 (s, 3H) ; 3.25 – 3.35 (m, 4H) ; 3.65 (s, 3H) ; 7.2 – 7.3 (m, 2H) ; 8 (m, 1H) ; 8.2 - 8.3 (m, 1H)

15 Solvent : CDCl<sub>3</sub>

- Compound 160 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 2.55 (s, 3H) ; 3.3 - 3.5 (m, 4H) ; 4.9 (m, 2H) ; 6.3 – 6.4 (m, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 – 7.4 (m, 6H) ; 8.1 (s, 1H) ; 8.35 (m, 1H)

20 Solvent : CDCl<sub>3</sub>

- Compound 161 :

<sup>1</sup>H NMR δ (ppm) : 2 (m, 4H) ; 3.4 (m, 4H) ; 4.8 (d, 2H) ; 6.35 – 6.4 (dt, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.4 (m, 4H) ; 7.45 (d, 2H) ; 7.55 (s, 1H) ; 8 (d, 1H) ; 10 (m, 1H)

25 Solvent : CDCl<sub>3</sub>

- Compound 162 :

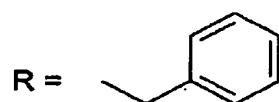
<sup>1</sup>H NMR δ (ppm) : 1.5 – 2.1 (m, 16H) ; 3.3 - 3.7 (m, 8H) ; 4.9 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 6.8 – 6.9 (d, 1H) ; 7.2 – 7.5 (m, 6H) ; 8.25 (d, 1H)

30 Solvent : CDCl<sub>3</sub>

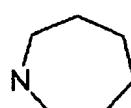
Example 163

METHOD A : 1-Azepanyl-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H ;



; NR4R5 =



35

4.0 g (10.7 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (prepared by the method of Example 256) suspended in 25 ml of hexamethylenimine are placed in a 50 ml round-bottomed flask protected from moisture.

The mixture is then refluxed with stirring for 16 hours.

5 After cooling, the solution obtained is concentrated under vacuum to give 4.8 g of residue which is purified by flash chromatography on a column of silica, eluting with a 99.6 CH<sub>2</sub>Cl<sub>2</sub> / 0.4 CH<sub>3</sub>OH mixture.

The TLC-pure fractions are combined and evaporated to dryness and the product obtained (4.0 g) is recrystallized from ethanol.

10 3.2 g of the compound of Example 163 are obtained in the form of crystals.

Yield = 66%.

m.p. (Tottoli) = 175° C

TLC (99 CH<sub>2</sub>Cl<sub>2</sub> / 1 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.40

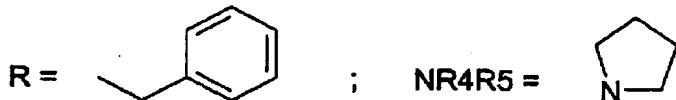
<sup>1</sup>H NMR δ (ppm) CDCl<sub>3</sub> :

15 1.7 – 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.45 –d, 2H) ; 8.0 (d, 1H) ; 8.15 (s, 1H) ; 8.4 (d, 1H)

#### Example 164

METHOD B : 1-(Pyrrolidin-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a] quinazolin-5-one.

20 (I) : X<sub>1</sub> = 7-Br ; X<sub>2</sub> = H ;



25 37.0 g (85 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one dissolved in 750 ml of dimethylformamide (DMF) are placed in a reactor protected from moisture and 14.3 g (340 mmol) of sodium bicarbonate are added, followed by 12.1 g (340 mmol) of pyrrolidine.

The mixture is then refluxed with stirring for 6 hours.

30 After cooling, the solvent is evaporated off under vacuum, the residue obtained is taken up in a water/ethyl acetate mixture and the insoluble material therein is triturated and then filtered and dried: 18.3g of a TLC-pure first crop of the compound of Example 164 are thus obtained.

35 The aqueous and organic phases are separated and the ethyl acetate phase is washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentrating the solvent under vacuum, 14.2 g of a second crop of the compound of Example 164, which is also TLC-pure, are obtained.

Yield (of crude product) = 90% ; the product is used for the next step without further purification.

A sample of 0.35 g is recrystallized from methanol to give 0.32 g of the pure compound in the form of crystals.

5 m.p. (Tottoli) = 173°C

TLC (99 CH<sub>2</sub>Cl<sub>2</sub>/1 CH<sub>3</sub>OH) = 0.35

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

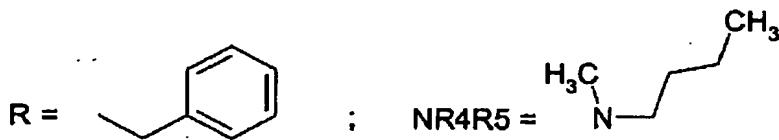
10

**Example 165**

**METHOD C** : 1-[N-(n-butyl)-N-methylamino]-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H

15



2.5 g (5.75 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 30 ml of ethanol are placed in a reactor under pressure. 5.0g of n-butylmethylamine (57.5 mmol) are added, the reactor is closed hermetically and it is then

20 heated on an oil bath at 160°C for 8 hours. After cooling and leaving to stand for 2 days, the residual oil (2.8 g) is chromatographed on a column of silica, eluting with a 99.5 CH<sub>2</sub>Cl<sub>2</sub> / 0.5 CH<sub>3</sub>OH mixture. 1.8 g of the compound of Example 165 are obtained.

Yield = 70%.

TLC (98.5 CH<sub>2</sub>Cl<sub>2</sub>/1.5 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.45

25 <sup>1</sup>H NMR δ (ppm) : 0.9 (t, 3H) ; 1.25 – 1.4 (m, 2H) ; 1.55 – 1.7 (m, 2H) ; 2.85 (s, 3H) ; 2.9 – 3.5 (m, 2H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

30

The compounds (I) of Examples 166 to 198 (Table 3) are prepared according to one of the methods A, B and C described in Examples 163 to 165.

TABLE 3

| Compound No. | X1   | R   | NR4R5 | Yield (%) | m.p. (°C) | Method |
|--------------|------|---|-------|-----------|-----------|--------|
| 166          | H    | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 70        | 167       | B      |
| 167          | 7-Cl | CH <sub>3</sub>                               |       | 17        | 112       | A      |
| 168          | 7-Cl | CH <sub>3</sub>                               |       | 35        | 192       | A      |
| 169          | 7-Cl | CH <sub>3</sub>                               |       | 50        | 180-182   | A      |
| 170          | 7-Cl | CH <sub>3</sub>                               |       | 60        | 185       | A      |
| 171          | 7-Cl | C <sub>6</sub> H <sub>5</sub>                 |       | 5         | 179       | A      |
| 172          | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 88        | 162       | A      |
| 173          | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 78        | 163       | B      |
| 174          | 7-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 68        | 178       | B      |
| 175          | 8-Cl | CH <sub>3</sub>                               |       | 11        | 179       | A      |
| 176          | 8-Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 1         | -         | B      |
| 177          | 7-Br | CH <sub>3</sub>                               |       | 72        | 174       | A      |
| 178          | 7-Br | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 67        | 183-185   | A      |
| 179          | 7-Br | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 53        | 171       | B      |
| 180          | 7-Br | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |       | 50        | 189       | B      |

| Compound No. | X1                 | R   | NR4R5             | Yield (%) | m.p. (°C) | Method |
|--------------|--------------------|---|-------------------|-----------|-----------|--------|
| 181          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 49        | 235       | B      |
| 182          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 60        | 230       | B      |
| 183          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 51        | 238       | B      |
| 184          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 50        | 226       | B      |
| 185          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 82        | 172       | B      |
| 186          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 85        | 210       | B      |
| 187          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 79        | 176       | B      |
| 188          | 7-Br               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> | NHCH <sub>3</sub> | 52        | 238       | C      |
| 189          | 7-I                | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 100       | 184       | B      |
| 190          | 7-CH <sub>3</sub>  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 90        | 183       | B      |
| 191          | 7-CH <sub>3</sub>  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 60        | 189       | B      |
| 192          | 7-CH <sub>3</sub>  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 75        | 186       | B      |
| 193          | 7-CH <sub>3</sub>  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 78        | 265       | B      |
| 194          | 8-CH <sub>3</sub>  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 50        | 202       | A      |
| 195          | 7-OCH <sub>3</sub> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 42        | 153       | B      |
| 196          | 7-OCH <sub>3</sub> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 65        | 154       | B      |
| 197          | 7-CN               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                   | 77        | 219       | B      |

| Compound No. | X1                | R   | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|-------------------|---|---|-----------|-----------|--------|
| 198          | 7-NO <sub>2</sub> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |  | 32        | 206       | A      |

- Compound 166 :

5      <sup>1</sup>H NMR δ (ppm) : 2 (m, 4H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.4 (d, 2H) ;  
7.6 (t, 1H) ; 7.9 (t, 1H) ; 8.2 (m, 2H)

Solvent : DMSO

- Compound 167 :

10     <sup>1</sup>H NMR δ (ppm) : 0.8 (m, 6H) ; 1.15 – 1.25 (m, 4H) ; 1.35 – 1.55 (m, 4H) ; 3 (m, 2H) ; 3.2 (m, 2H) ; 3.7 (s, 3H) ; 7.65 (m, 1H) ; 8.3 (m, 1H) ; 8.45 (m, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 168 :

15     <sup>1</sup>H NMR δ (ppm) : 1.3-1.9 (m, 6H) ; 2.9 (t, 2H) ; 3.3 (m, 2H) ; 3.5 (s, 3H) ; 8.0 (d, 1H) ; 8.1 (d, 1H) ; 8.3 (d, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 170 :

20     <sup>1</sup>H NMR δ (ppm) : 0.7 (s, 3H) ; 0.8 (s, 3H) ; 1.0 (s, 3H) ; 1.5-1.9 (m, 5H) ; 2.55 (d, 1H) ; 2.85 (d, 1H) ; 3.15 (m, 4H) ; 3.4 (m, 4H) ; 7.9 (d, 1H) ; 8.0 (s, 1H) ; 8.4 (m, 1H)

Solvent : DMSO

- Compound 171 :

25     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.8 (m, 8H) ; 3.3 (m, 4H(+H<sub>2</sub>O) ; 7.45 – 7.6 (m, 5H) ; 8.05 (m, 1H) ; 8.15 (s, 1H) ; 8.45 (d, 1H)

Solvent : DMSO

- Compound 172 :

30     <sup>1</sup>H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H) ; 5.3 (s, 2H) ; 7.25 – 7.5 (m, 5H) ; 8.0 (m, 1H) ; 8.15 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- Compound 173 :

<sup>1</sup>H NMR δ (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.65 – 7.75 (m, 3H) ; 8.2 (dd, 1H) ; 8.35 (s, 1H)

Solvent : CDCl<sub>3</sub>

5

- Compound 174 :

<sup>1</sup>H NMR δ (ppm) : 1.4 – 1.6 (m, 1H) ; 1.7 – 2 (m, 4H) ; 3 – 3.15 (m, 2H) ; 3.3 – 3.45 (m, 2H) ; 5.45 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.7 – 7.8 (m, 3H) ; 8.3 – 8.4 (m, 2H)

Solvent : CDCl<sub>3</sub>

10

- Compound 175 :

<sup>1</sup>H NMR δ (ppm) : 1.85 – 1.95 (m, 4H) ; 3.4 (m, 4H + H<sub>2</sub>O) ; 3.65 (s, 3H) ; 7.7 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)

Solvent : DMSO

15

- Compound 176 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.4 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.4 – 7.45 (m, 2H) ; 7.65 – 7.7 (m, 2H) ; 8.25 – 8.3 (m, 2H) ; 8.6 (s, 1H)

Solvent : CDCl<sub>3</sub>

20

- Compound 177 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.4 (m, 4H) ; 3.7 (s, 3H) ; 7.75 (m, 1H) ; 8.25 (m, 1H) ; 8.4 (m, 1H)

Solvent : CDCl<sub>3</sub>

25

- Compound 178 :

<sup>1</sup>H NMR δ (ppm) : 1.35 – 1.95 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (d, 2H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.75 (d, 2H) ; 7.95 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

30

- Compound 179 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

35

- Compound 180 :

<sup>1</sup>H NMR δ (ppm) : 3.2 – 3.4 (m, 4H) ; 3.75 – 3.9 (m, 2H) ; 3.9 – 4.1 (m, 2H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 181 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 2.8 – 3.0 (m, 4H) ; 3.35 – 3.5 (m, 2H) ; 3.5 – 3.7 (m, 2H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 182 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 2.3 – 2.45 (m, 5H) ; 2.9 – 3.0 (m, 2H) ; 3.25 – 3.35 (m, 4H) ; 5.5 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 183 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 3.0 – 3.2 (m, 2H) ; 3.35 – 3.5 (m, 4H) ; 3.6 – 3.75 (m, 2H) ; 5.5 (s, 2H) ; 6.9 – 7.05 (m, 3H) ; 7.2 – 7.35 (m, 5H) ; 7.7 (d, 2H) ; 7.85 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 184 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 2.4 (m, 2H) ; 3 (m, 2H) ; 3.3 (m, 4H) ; 5.5 (s, 2H) ; 7.3 (m, 8H) ; 7.7 (m, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 185 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 2.2 – 2.65 (m, 2H) ; 3.2 – 3.9 (m, 4H) ; 5.45 (s, 2H) ; 5.8 – 5.9 (m, 1H) ; 5.9 – 6.0 (m, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

30 - Compound 186 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 4.3 (s, 4H) ; 5.5 (s, 2H) ; 5.95 (s, 2H) ; 7.25 – 7.4 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

35 - Compound 187 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 2 – 2.1 (m, 1H) ; 2.3 – 2.4 (m, 1H) ; 3.2 – 3.6 (m, 5H) ; 4.6 – 4.7 (m, 1H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.65 (d, 1H) ; 7.85 (d, 1H) ; 8.3 (d, 2H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 188 :

<sup>1</sup>H NMR δ (ppm) : 3.05 (s, 3H) ; 3.9 – 4.0 (m, 1H) ; 5.35 (s, 2H) ; 7.15 – 7.25 (m, 3H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 7.95 (d, 1H) ; 8.4 (s, 1H)

5 Solvent : CDCl<sub>3</sub>

- Compound 189 :

<sup>1</sup>H NMR δ (ppm) : 2 (m, 4H) ; 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.4 (m, 2H) ; 8.0 (m, 1H) ; 8.2 (m, 1H) ; 8.5 (m, 1H)

10 Solvent : DMSO

- Compound 190 :

<sup>1</sup>H NMR δ (ppm) : 1.75 – 1.95 (m, 8H) ; 2.45 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.45 (dd, 1H) ; 7.7 (dd, 2H) ; 8.15 (s, 1H) ; 8.3 (d, 1H)

15 Solvent : CDCl<sub>3</sub>

- Compound 191 :

<sup>1</sup>H NMR δ (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 – 7.55 (m, 5H) ; 7.7 (d, 1H) ; 8 (s, 1H) ; 8.15 (d, 1H)

20 Solvent : CDCl<sub>3</sub>

- Compound 192 :

<sup>1</sup>H NMR δ (ppm) : 2.45 (s, 3H) ; 2.9 (s, 6H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.45 (d, 1H) ; 7.7 (d, 2H) ; 8.2 (d, 2H)

25 Solvent : CDCl<sub>3</sub>

- Compound 193 :

<sup>1</sup>H NMR δ (ppm) : 2.5 (s, 3H) ; 2.8 – 3.05 (m, 4H) ; 3.35 – 3.75 (m, 4H) ; 5.5 (s, 2H) ; 7.15 – 7.4 (m, 3H) ; 7.6 (d, 1H) ; 7.7 (d, 2H) ; 8.1 – 8.25 (m, 2H)

30 Solvent : CDCl<sub>3</sub>

- Compound 194 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 2.55 (s, 3H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.25 – 7.35 (m, 4H) ; 7.7 (m, 2H) ; 8.25 (m, 2H)

35 Solvent : CDCl<sub>3</sub>

5 - Compound 195 :

<sup>1</sup>H NMR δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.35 – 3.40 (m, 4H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 7.25 – 7.35 (m, 4H) ; 7.7 (dd, 2H) ; 7.8 (d, 1H) ; 8.35 (d, 1H)

Solvent : CDCl<sub>3</sub>

10 - Compound 196 :

<sup>1</sup>H NMR δ (ppm) : 2 (m, 4H) ; 3.35 (m, 4H) ; 3.9 (s, 3H) ; 5.35 (s, 2H) ; 7.25 – 7.35 (m, 3H) ; 7.45 (d, 2H) ; 7.55 (d, 1H) ; 7.7 (s, 1H) ; 8.2 (d, 1H)

Solvent : DMSO

15 - Compound 197 :

<sup>1</sup>H NMR δ (ppm) : 2.4 (m, 4H) ; 3.2 (m, 4H) ; 5.2 (s, 2H) ; 7.1 – 7.25 (m, 3H) ; 7.35 (m, 2H) ; 8.25 (m, 2H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

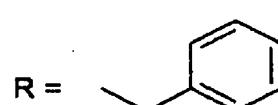
20 - Compound 198 :

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H + H<sub>2</sub>O) ; 5.35 (s, 2H) ; 7.3 (m, 3H) ; 7.5 (m, 2H) ; 8.55 (d, 1H) ; 8.75 (d, 1H) ; 8.9 (s, 1H)

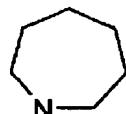
Solvent : DMSO

25 Example 199 : 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

(I) : X1 = 7-Cl ; X2 = H



; NR4R5 =



30

0.44 g (1.27 mmol) of 4-benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 254) suspended in 2.5 ml of hexamethyleneimine is placed in a 50 ml round-bottomed flask fitted with a stirrer and a condenser. The mixture is refluxed for 16 hours with stirring. The brown solution obtained is then left to stand at room temperature until it has cooled completely; it is poured into a mixture of water and methylene chloride, the mixture is stirred and the 2 phases are separated by settling. The organic phase is washed twice with water, dried over Na<sub>2</sub>SO<sub>4</sub> and then evaporated under vacuum to give 0.59 g of a solid brown residue.

35

This product is chromatographed on a column of silica, eluting with a 99.5 CH<sub>2</sub>Cl<sub>2</sub> / 0.5 CH<sub>3</sub>OH mixture.

After combining and evaporating the TLC-pure fractions, 0.46 g of the compound of Example 199 is obtained. This product is recrystallized from ethanol to give 0.4 g of colourless crystals.

Yield = 77%

5 m.p. (Tottoli) = 162°C

TLC (98.5 CH<sub>2</sub>Cl<sub>2</sub> / 1.5 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.35

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 (s, 4H) ; 5.3 (s, 2H) ; 7.25 – 7.5 (m, 5H) ; 8.0 (m, 1H) ; 8.15 (d, 1H) ; 8.4 (d, 1H)

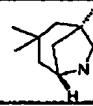
Solvent : DMSO

10 Compounds (I) of Examples 200 to 214 (Table 4) are prepared according to the process of Example 199.

TABLE 4

15

| Compound No. | X1   | R   | NR4R5   | Yield (%) | m.p. (°C) | Method |
|--------------|------|---|---|-----------|-----------|--------|
| 200          | H    | CH <sub>3</sub>                               |   | 40        | 199 – 203 | A      |
| 201          | H    | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |  | 66        | 157       | A      |
| 202          | 6-Cl | CH <sub>3</sub>                               |  | 8.5       | > 275     | A      |
| 203          | 7-Cl | CH <sub>3</sub>                               |  | 77        | 145       | A      |
| 204          | 7-Cl | CH <sub>3</sub> CH <sub>2</sub>               |  | 11        | 98-100    | A      |
| 205          | 7-Cl | CH <sub>3</sub>                               |  | 50        | 203-205   | A      |
| 206          | 7-Cl | CH <sub>3</sub>                               |  | 25        | 232       | A      |
| 207          | 7-Cl | CH <sub>3</sub>                               |  | 25        | 123-125   | A      |
| 208          | 7-Cl | CH <sub>3</sub>                               |  | 15        | 204       | A      |
| 209          | 7-Cl | CH <sub>3</sub>                               |  | 30        | 272       | A      |

| Compound No. | X1     | R   | NR4RS   | Yield (%) | m.p. (°C) | Method |
|--------------|--------|-----|---|-----------|-----------|--------|
| 210          | 7-Cl   | CH3 |  | 25        | 180       | A      |
| 211          | 7-Cl   | CH3 |  | 25        | 165       | A      |
| 212          | 7-F    | CH3 |  | 13        | 136       | A      |
| 213          | 7-I    | CH3 |  | 47        | 206       | A      |
| 214          | 7-OCH3 | CH3 |  | 34        | 203       | A      |

- Compound 200 :

<sup>1</sup>H NMR δ (ppm) : 1.75-1.9 (m, 8H) ; 3.4 (m, 4H) ; 3.6 (s, 3H) ; 7.6 (t, 1H) ; 8 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

5 Solvent : DMSO

- Compound 201 :

<sup>1</sup>H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 7.2 - 7.35 (m, 3H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.2 (d, 1H) ; 8.4 (d, 1H)

10 Solvent : DMSO

- Compound 202 :

<sup>1</sup>H NMR δ (ppm) : 1.5 - 1.8 (m, 8H) ; 3.4 (m, 4H) ; 3.5 (s, 3H) ; 7.05 (d, 1H) ; 7.5 (t, 1H) ; 8.4 (d, 1H)

15 Solvent : DMSO

- Compound 203 :

<sup>1</sup>H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (m, 4H) ; 3.5 (s, 3H) ; 7.95 (d, 1H) ; 8.1 (s, 1H) ; 8.35 (d, 1H)

20 Solvent : DMSO

- Compound 204 :

<sup>1</sup>H NMR δ (ppm) : 1.3 (t, 3H) ; 1.7 - 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.15 (q, 2H) ; 7.95 (d, 1H) ; 8.1 (s, 1H) ; 8.35 (d, 1H)

25 Solvent : DMSO

- Compound 205 :

<sup>1</sup>H NMR δ (ppm) : 2.0 (m, 4H) ; 3.35 (m, 4H) ; 3.75 (s, 3H) ; 7.65 (d, 1H) ; 8.15 (d, 1H) ; 8.3 (s, 1H)

5 Solvent : CDCl<sub>3</sub>

- Compound 206 :

<sup>1</sup>H NMR δ (ppm) : 3.1 - 3.35 (m, 4H) ; 3.65 (s, 3H) ; 3.85 (m, 2H) ; 4.0 (m, 2H) ; 7.75 (d, 1H) ; 8.35 (m, 2H)

10 Solvent : CDCl<sub>3</sub>

- Compound 207 :

<sup>1</sup>H NMR δ (ppm) : 1.8 (m, 10H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

15 Solvent : CDCl<sub>3</sub>

- Compound 208 :

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 2H) ; 2.8 - 3.1 (m, 2H) ; 3.65 (m, 1H) ; 3.75 (s, 3H) ; 3.9 (m, 1H) ; 6.15 (d, 1H) ; 6.75 (t, 1H) ; 6.85 (t, 1H) ; 7.1 (d, 1H) ; 7.5 (d, 1H) ; 7.85 (d, 1H) ;

20 8.3 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 209 :

<sup>1</sup>H NMR δ (ppm) : 2.9 (m, 1H) ; 3.2 (m, 1H) ; 3.4 (m, 1H) ; 3.6 (m, 1H) ; 3.7 (s, 3H) ; 4.3

25 (d, 1H) ; 4.45 (d, 1H) ; 7.05 (d, 1H) ; 7.2 (m, 3H) ; 7.6 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)

Solvent : CDCl<sub>3</sub>

- Compound 210 :

<sup>1</sup>H NMR δ (ppm) : 1.4 (m, 2H) ; 1.7 (m, 3H) ; 2.6 (d, 2H) ; 2.9 - 3.15 (m, 2H) ; 3.3-3.5 (m,

30 2H) ; 3.65 (s, 3H) ; 7.0-7.35 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (m, 2H)

Solvent : CDCl<sub>3</sub>

- Compound 211 :

<sup>1</sup>H NMR δ (ppm) : 1 (s, 3H) ; 1.1 (s, 3H) ; 1.25-1.4 (m, 5H) ; 1.45 (d, 1H) ; 1.6 (m, 2H) ;

35 1.9 (d, 1H) ; 2.05 (m, 1H) ; 3.35 (d, 1H) ; 3.45 (d, 1H) ; 3.7 (s, 3H) ; 4 (m, 1H) ; 7.65 (d, 1H) ; 8.3 (s, 1H) ; 8.6 (d, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 212 :**

<sup>1</sup>H NMR δ (ppm) : 1.7 – 1.8 (m, 8H) ; 3.3 (m, 4H (+H<sub>2</sub>O)) ; 3.5 (s, 3H) ; 7.8 (m, 1H) ; 7.9 (m, 1H) ; 8.4 (m, 1H)

Solvent : DMSO

5

**- Compound 213 :**

<sup>1</sup>H NMR δ (ppm) : 1.7 - 1.9 (m, 8H) ; 3.3 (m, 4H) ; 3.7 (s, 3H) ; 8.0 (d, 1H) ; 8.1 (d, 1H) ; 8.65 (s, 1H)

Solvent : CDCl<sub>3</sub>

10

**- Compound 214 :**

<sup>1</sup>H NMR δ (ppm) : 1.7 - 1.85 (m, 8H) ; 3.3 (s, 4H) ; 3.5 (s, 3H) ; 3.9 (s, 3H) ; 7.5 (d, 1H) ; 7.6 (s, 1H) ; 8.3 (d, 1H)

Solvent : CDCl<sub>3</sub>

15

**Example 215 :** 4-Benzyl-7-bromo-1-(N-ethyl-N-methylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

20 0.3 g (0.8 mmol) of 4-benzyl-7-bromo-1-(N-methylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 188) is dissolved in 5 ml of DMF. 0.135 g (0.85 mmol) of methyl iodide and 0.13 g (0.93 mmol) of potassium carbonate are added. The mixture obtained is stirred at room temperature overnight and then heated at 100°C for 6 hours. After cooling, the solvent is evaporated off under vacuum and the residue is taken up in water and ethyl acetate. The organic phase is separated out by settling, washed with 25 saturated sodium chloride solution, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. 0.3 g of crude product is obtained, which is purified by chromatography on a column of silica, eluting with a 99 CH<sub>2</sub>Cl<sub>2</sub> / 1 CH<sub>3</sub>OH mixture. The fractions containing the desired product are combined and concentrated under vacuum, and the residue is then recrystallized from methanol to give 0.05 g of pure compound of Example 215.

30 Yield = 22%

m.p. (Tottoli) = 148°C

TLC (98.5 CH<sub>2</sub>Cl<sub>2</sub> / 1.5 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.45

<sup>1</sup>H NMR δ (ppm) : 1.25 (t, 3H) ; 2.9 (s, 3H) ; 3.2 – 3.4 (m, 2H) ; 5.45 (s, 2H) ; 7.2 – 7.35 (m, 3H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

35 Solvent : CDCl<sub>3</sub>

**Example 216 : 4-Benzyl-1-(N,N-diethyl)-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

5      2.3g (5.87 mmol) of 4-benzyl-7-methyl-1-(thiamorpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 193) are suspended in 250 ml of ethanol. A catalytic amount of Raney nickel is added and the mixture is refluxed for 24 hours with stirring. The catalyst is removed by filtration through Celite and the alcoholic solution is concentrated under vacuum: 1.6 g of crude product are obtained, which product is purified by chromatography on a column of silica, eluting with  $\text{CH}_2\text{Cl}_2$  and a methanol gradient from 99.5/0.5 to give 0.9 g of TLC-pure product. A sample is recrystallized from ethanol for the determination of the physical constants.

10     Yield = 42%

15     m.p. (Tottoli) = 154°C

20     TLC (99  $\text{CH}_2\text{Cl}_2$  / 1  $\text{CH}_3\text{OH}$ ) :  $R_f$  = 0.35

25      $^1\text{H NMR}$   $\delta$  (ppm) : 1 - 1.3 (m, 6H) ; 2.4 (s, 3H) ; 2.9 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 – 7.3 (m, 3H) ; 7.45 (d, 1H) ; 7.6 (d, 2H) ; 8.15 (s, 1H) ; 8.3 (d, 1H)

30     Solvent :  $\text{CDCl}_3$

**Example 217 : 4-Benzyl-7-bromo-1-(pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

20     0.7g (1.8 mmol) of 1-amino-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (intermediate compound 10 of Example 271) suspended in 5 ml of acetic acid is placed in a 25 ml round-bottomed flask. 0.25g (1.9 mmol) of 2,5-dimethoxytetrahydrofuran is added and the mixture is then refluxed for 1 hour. After cooling and evaporation of the acetic acid under vacuum, 0.8 g of a highly coloured solid is obtained, which is purified by chromatography on a column of silica, eluting with a  $\text{CH}_2\text{Cl}_2$  /  $\text{CH}_3\text{OH}$  mixture (99.4/0.6 then 99/1). The solid obtained from the pure fractions is recrystallized from ethanol to give 0.45 g of the compound of example 217.

30     Yield = 55%

35     m.p. (Tottoli) = 214°C

40     TLC (99  $\text{CH}_2\text{Cl}_2$  / 1  $\text{CH}_3\text{OH}$ ) :  $R_f$  = 0.5

45      $^1\text{H NMR}$   $\delta$  (ppm) : 5.55 (s, 2H) ; 5.8 (d, 1H) ; 6.5 (s, 2H) ; 6.9 (s, 2H) ; 7.25 – 7.4 (m, 3H) ; 7.7 (d, 1H) ; 7.75 (d, 2H) ; 8.55 (s, 1H)

50     Solvent :  $\text{CDCl}_3$

**Example 218 :** 4-(4-Aminobenzyl)-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.45g (0.96 mmol) of 7-bromo-4-(4-nitrobenzyl)-1-(pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (compound of Example 48) in 10 ml of ethanol is loaded into a 50 ml round-bottomed flask. 1.08g (24 mmol) of stannous chloride dihydrate are added and the mixture is then heated at 70°C for 30 minutes with stirring. After cooling, the mixture is poured into ice-cold water. It is extracted several times with ethyl acetate with a small amount of CHCl<sub>3</sub>, the organic phase is washed with saturated sodium chloride solution, dried over Na<sub>2</sub>SO<sub>4</sub> then concentrated under vacuum. The solid residue obtained (0.35 g) is washed with methanol (50 ml) to give 0.25 g of TLC-pure product.

Yield = 83%

m.p. (Tottoli) = 263°C

TLC (98 CH<sub>2</sub>Cl<sub>2</sub> / 2 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.25

<sup>1</sup>H NMR δ (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5 (s, 2H) ; 5.1 (s, 2H) ; 6.5 (d, 2H) ; 7.2 (d, 2H) ; 8.1 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)

Solvent : DMSO

**Example 219 :** 4-(Benzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

**Example 219-1/** 4-Benzyl-7-(4-tolylsulphonyloxy)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1.46g (5 mmol) of 4-benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (intermediate obtained by the method of Example 255) in 15 ml of dry methylene chloride are loaded into a reactor equipped with a stirring system. 0.95 g (5 mmol) of tosyl chloride is added, after which 1 ml (7.5 mmol) of triethylamine is added over 5 minutes with stirring, the reaction being slightly exothermic. After stirring at room temperature for a further 2 hours, the organic solution obtained is washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> to give, after evaporation of the solvent, a coloured amorphous residue which is purified by chromatography on a column of silica, eluting with ethyl acetate. 1.9 g of TLC-pure product are obtained. This product is used for the next step without further purification.

Yield = 85%

2/ Example 219-2/ 4-Benzyl-1-bromo-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.4g of this compound is obtained from 0.45 g of 4-benzyl-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 219-1) by the bromination method described in Example 256.

Yield = 76%

3/ Example 219-3/ 4-Benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.83 g of bromo derivative obtained in Example 219-2 is treated with pyrrolidine, under the conditions of Example 164. After treatment, 1.0 g of a crude mixture of 2 major compounds is obtained, which compounds are separated by chromatography on a column of silica, eluting with a 98 CH<sub>2</sub>Cl<sub>2</sub> / 2 CH<sub>3</sub>OH mixture. The fractions containing the first pure product are combined and concentrated to give 0.375 g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 45%

The fractions containing the second pure product are combined and evaporated under vacuum to give 0.12g of 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 15%

m.p. (Tottoli) = 287°C

<sup>1</sup>H NMR δ (ppm) : 1.95 (m, 4H) ; 3.3 (m, 4H) ; 7.3 (s, 2H) ; 7.2 – 7.6 (m, 7H) ; 8.1 (d, 1H) ; 10.2 (s, 1H)

25 Solvent : DMSO

**Example 220** : 4-(4-Cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1/ Example 220-1/ 1-(Pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1.3 g of this compound are obtained from 2.4 g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 219-3) by the debenzylation method described in Example 263.

Yield = 68%

2/ Example 220-2/ 4-(4-Cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.48 g of this compound is obtained from 0.66 g of 1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 220-1) by the  
5 N-alkylation method described in Example 3.

Yield = 52%

3/ Example 220-3/ 4-(4-Cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.

10 0.3 g (0.55 mmol) of 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulphonyloxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 220-2) is dissolved in 1 ml of dry DMF. 0.27 ml of pyrrolidine (2.75 mmol) is added and the mixture is then heated at 140°C for 6 hours with stirring. The solvent is evaporated off under vacuum and the residue is taken up in a mixture of ethyl acetate / aqueous N hydrochloric acid solution.  
15 The insoluble material is separated out by filtration, washed with water to neutral pH and dried under vacuum; 0.13 g of crude product is obtained, which is crystallized from 5 ml of ethanol, filtered and dried to give 0.085 g of pure product.

Yield = 40%

m.p. (Tottoli) = 305°C

20  $^1\text{H}$  NMR  $\delta$  (ppm) : 2 (m, 4H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.35 (d, 1H) ; 7.6 – 7.7 (m, 3H) ; 7.8 (d, 2H) ; 8.1 (d, 1H) ; 10.2 (s, 1H)

Solvent : DMSO

Example 221 : 7-Acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

1/ Example 221-1/ 7-Acetamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.45 g of this compound is obtained from 0.5 g of 7-acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one by the bromination method described in Example 256.

Yield = 72%

2/ Example 221-2/ 7-Acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

35 8.7 g (21 mmol) of the bromo derivative obtained in Example 221-1 are treated with 3.7 ml (42 mmol) of pyrrolidine and 3.54 g (42 mmol) of sodium bicarbonate in 80 ml of DMF, under the conditions of Example 164. After treatment, 8.0 g of crude product are obtained,

which product is purified by chromatography on a column of silica, eluting with a 98 CH<sub>2</sub>Cl<sub>2</sub> / 2 CH<sub>3</sub>OH mixture. The fractions containing the pure product are combined and concentrated and the residue is then crystallized from ethanol to give 6.6 g of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

5 Yield = 78 %

m.p. (Tottoli) = 265°C

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 2.25 (s, 3H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (m, 3H) ; 7.6 (d, 2H) ; 8.1 (s, 1H) ; 8.2 (m, 2H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

10

**Example 222 :** 7-Acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Starting with 1.2 g (3.0 mmol) of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 221), debenzylated to 7-acetamido-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one by the method with palladium/C described in Example 257 and then treated directly with 0.59 g of cinnamyl bromide in the presence of 0.98 g of caesium carbonate in 15 ml of DMF, according to the method described in Example 3, and after purification by chromatography on a column of silica and recrystallization from ethanol, 0.4 g of the pure compound of Example 222 is obtained.

Yield = 31%.

m.p. (Tottoli) = 248°C

TLC (95 CH<sub>2</sub>Cl<sub>2</sub> / 5 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.30

25 <sup>1</sup>H NMR δ (ppm) CDCl<sub>3</sub> :

2.0-2.1 (m, 4H) ; 2.25 (s, 3H) ; 3.45 (m, 4H) ; 5 (d, 2H) ; 6.35-6.4 (dt, 1H) ; 6.8 (d, 1H) ; 7.15-7.35 (m, 5H) ; 8.1 (s, 1H) ; 8.2-8.3 (m, 2H) ; 8.4 (m, 1H)

30 **Example 223 :** 7-Amino-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

0.2 g (0.46 mmol) of 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 222) in 5 ml of a 6N hydrochloric acid solution is placed in a 20 ml round-bottomed flask and refluxed for 15 minutes with stirring. After cooling, the solution obtained is basified with sodium hydroxide solution and extracted 3 times with methylene chloride. The combined organic phases are washed with saturated NaCl solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and then evaporated under

vacuum. The crude product (0.12 g) is recrystallized from ethanol to give 0.08 g of the pure compound of Example 223.

Yield = 44%

m.p. (Tottoli) = 199°C

5  $^1\text{H}$  NMR  $\delta$  (ppm)  $\text{CDCl}_3$ :

2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.0 (m, 2H) ; 5.1 (d, 2H) ; 6.5-6.6 (dt, 1H) ; 6.85 (d, 1H) ; 7.0-7.3 (m, 3H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H) ; 8.6 (s, 1H).

10 The compounds of general formula (I) of Examples 224 to 233 in Table 5 are prepared by the method of Example 223.

TABLE 5

| Compound No. | X1                                 | R  | NR4R5  | Yield (%) | m.p. (°C) |
|--------------|------------------------------------|--|--|-----------|-----------|
| 224          | 7-NH <sub>2</sub>                  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>          |    | 40        | 240 (dec) |
| 225          | 7-NH <sub>2</sub>                  | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>          |   | 60        | 230       |
| 226          | 7-NH <sub>2</sub>                  | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>      |  | 67        | 152       |
| 227          | 7-NH <sub>2</sub>                  | (E) (3-pyridyl)-CH=CHCH <sub>2</sub>                   |  | 70        | 201       |
| 228          | 7-NH <sub>2</sub>                  | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>      |  | 68        | 163       |
| 229          | 7-NH <sub>2</sub>                  | (E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> |  | 67        | 198       |
| 230          | 7-CH <sub>3</sub> NH               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>          |  | 58        | 171       |
| 231          | 7-CH <sub>3</sub> NH               | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>      |  | 91        | 270       |
| 232          | 8-CH <sub>3</sub> NH               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>          |  | 76        | -         |
| 233          | 7-C <sub>2</sub> H <sub>5</sub> NH | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>          |  | 67        | 225       |

**- Compound 224 :**

<sup>1</sup>H NMR δ (ppm) : 1.8 – 1.9 (m, 8H) ; 3.4 – 3.45 (m, 4H) ; 4 (s, 2H) ; 5.4 (s, 2H) ; 7 (m, 1H) ; 7.25 – 7.35 (m, 3H) ; 7.55 (s, 1H) ; 7.65 – 7.80 (m, 2H) ; 8.15 – 8.2 (m, 1H)

Solvent : CDCl<sub>3</sub>

5

**- Compound 225 :**

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4 (s, 2H) ; 5.45 (s, 2H) ; 7 (d, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.6 (s, 1H) ; 7.7 – 7.8 (d, 2H) ; 8 – 8.1 (d, 1H)

Solvent : CDCl<sub>3</sub>

10

**- Compound 226 :**

<sup>1</sup>H NMR δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 4.05 (s, 2H) ; 8.5 (s, 2H) ; 7.05 (m, 1H) ; 7.4 – 7.5 (m, 3H) ; 7.8 (s, 1H) ; 8.05 (d, 1H)

Solvent : CDCl<sub>3</sub>

15

**- Compound 227 :**

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4 (m, 2H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.05 (m, 1H) ; 7.2 – 7.3 (m, 2H) ; 7.35 (d, 2H) ; 7.6 (s, 1H) ; 8.1 (d, 1H)

Solvent : CDCl<sub>3</sub>

20

**- Compound 228 :**

<sup>1</sup>H NMR δ (ppm) : 2.8 (s, 6H) ; 5.4 (s, 2H) ; 5.7 (m, 2H) ; 7.10 – 7.15 (m, 1H) ; 7.4 (s, 1H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 8.05 (d, 1H)

Solvent : DMSO

25

**- Compound 229 :**

<sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 4.95 (d, 2H) ; 5.75 (m, 2H) ; 6.45 – 6.5 (dt, 1H) ; 6.7 – 6.8 (d, 1H) ; 7.2 (m, 1H) ; 7.25 – 7.4 (m, 6H) ; 8.1 (d, 1H)

Solvent : DMSO

30

**- Compound 230 :**

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 2.95 (s, 3H) ; 3.4 (m, 4H) ; 4.1 (m, 1H) ; 5.4 (s, 2H) ; 6.95 (d, 1H) ; 7.3 (m, 3H) ; 7.45 (s, 1H) ; 7.75 (dd, 2H) ; 8.1 (d, 1H)

Solvent : CDCl<sub>3</sub>

35

**- Compound 231 :**

<sup>1</sup>H NMR δ (ppm) : 2.1 (m, 4H) ; 2.9 (s, 3H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7 (m, 1H) ; 7.45 (s, 1H) ; 7.6 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (d, 1H)

Solvent :  $\text{CDCl}_3$

- Compound 232 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 1.9 - 2 (m, 4H) ; 2.85 (d, 3H) ; 3.3 (m, 4H) ; 5.3 (s, 2H) ; 6.7 (d, 1H) ;  
5 7.2 (q, 1H) ; 7.25 - 7.45 (m, 6H) ; 7.9 (d, 1H)

Solvent : DMSO

- Compound 233 :

$^1\text{H}$  NMR  $\delta$  (ppm) : 1.3 (t, 3H) ; 2.1 (m, 4H) ; 3.25 (m, 2H) ; 3.4 (m, 4H) ; 3.9 (m, 1H) ;  
10 5.45 (s, 2H) ; 7 (m, 1H) ; 7.2 - 7.3 (m, 3H) ; 7.45 (s, 1H) ; 7.7 (m, 2H) ; 8.1 (d, 1H)

Solvent :  $\text{CDCl}_3$

**Example 234 :** 4-Benzyl-7-(N-isopropylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

15 0.31 g (0.86 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 10 ml of methylene chloride is placed in a 20 ml round-bottomed flask. 0.14 ml (1.9 mmol) of acetone, 0.115 ml (1.9 mmol) of pure acetic acid and then 0.546 g (2.6 mmol) of sodium triacetoxyborohydride are added. The mixture is stirred at room temperature under a 20 nitrogen atmosphere for 48 hours. The solvent is evaporated off under vacuum and the residue is taken up in ethyl acetate. The organic phase is washed with sodium bicarbonate solution and then with saturated NaCl solution. After drying ( $\text{Na}_2\text{SO}_4$ ) and removal of the solvent under vacuum, 0.3 g of crude product is obtained, which is purified by chromatography on a column of silica, eluting with a 98  $\text{CH}_2\text{Cl}_2$  / 2  $\text{CH}_3\text{OH}$  mixture to 25 give 0.2 g of the TLC-pure compound of Example 234.

Yield = 58%

m.p. (Tottoli) = 208°C [EtOH]

$^1\text{H}$  NMR  $\delta$  (ppm) : 1.2 (m, 6H) ; 2.05 (m, 4H) ; 3.4 (m, 4H) ; 3.7 - 3.85 (m, 2H) ; 5.5 (s, 2H) ; 6.9 (m, 1H) ; 7.2 - 7.3 (m, 3H) ; 7.4 (s, 1H) ; 7.7 (m, 2H) ; 8.1 (m, 1H)

30 Solvent :  $\text{CDCl}_3$

**Example 235:** 4-Benzyl-7-methylsulphonylamino-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one and **Example 247 :** 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

35 0.55 g (1.5 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 10 ml of methylene chloride is placed in a 20 ml round-bottomed flask. 0.42 ml (3.0 mmol) of triethylamine is added, followed by 0.24 ml (3.0 mmol) of methanesulphonyl chloride. The solution obtained is

stirred at room temperature for 24 hours. After cooling, the solution obtained is washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and then evaporated under vacuum. The crude mixture of the 2 compounds obtained (0.85 g) is chromatographed on a column of silica, eluting with a 99  $\text{CH}_2\text{Cl}_2$  / 1  $\text{CH}_3\text{OH}$  / 0.1  $\text{NH}_4\text{OH}$  mixture. The fractions containing the first product by order of elution are combined and evaporated under vacuum to give 0.65 g of 4-benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

5 m.p. (Tottoli) = 221°C  
10  $^1\text{H}$  NMR  $\delta$  (ppm) DMSO : 2.2 – 2.3 (m, 4H) ; 2.9 (s, 3H) ; 3.15 (m, 4H) ; 5.15 (s, 2H) ; 7.1 – 7.2 (m, 3H) ; 7.25 (m, 2H) ; 7.5 – 7.6 (d, 1H) ; 7.85 (s, 1H) ; 8.05 – 8.1 (d, 1H) ; 10.05 (s, 1H)

15 The fractions containing the second product by order of elution are treated in a similar manner to give 0.15 g of 4-benzyl-7-methylsulphonylamino-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

Yield = 23%  
20 m.p. (Tottoli) = 283°C [EtOH]  
10  $^1\text{H}$  NMR  $\delta$  (ppm) DMSO : 2 (m, 4H) ; 3.45 (m, 4H) ; 3.5 (s, 3H) ; 5.45 (s, 2H) ; 7.3 (m, 3H) ; 7.7 (m, 3H) ; 6.35 (m, 2H)

25 Example 236 : 7-(N,N-Dimethylamino)-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-one.  
0.75g (2.05 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (described in Example 225) suspended in 0.8 ml of formic acid and 0.8 ml of formaldehyde are placed in a round-bottomed flask. The mixture is heated at 100°C for 1 hour with stirring. After cooling, the solution obtained is poured into ice-cold water and the suspension is extracted several times with ethyl acetate; the combined organic phases are washed with saturated aqueous sodium chloride solution, dried over  $\text{Na}_2\text{SO}_4$  and the concentrated under vacuum.

30 The crude product obtained (0.8 g) is purified by chromatography on a column of silica, eluting with a 98 methylene chloride / 2 methanol mixture. 0.23 g of the TLC-pure product of Example 236 is obtained.

35 Yield = 29%  
m.p. (Tottoli) = 194°C [EtOH]  
TLC (97  $\text{CH}_2\text{Cl}_2$  / 3  $\text{CH}_3\text{OH}$ ) :  $R_f$  = 0.65  
 $^1\text{H}$  NMR  $\delta$  (ppm) : 2.1 (m, 4H) ; 3.05 (s, 6H) ; 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.1 (m, 1H) ; 7.3 (m, 3H) ; 7.6 (d, 1H) ; 7.75 (m, 2H) ; 8.1 (d, 1H)  
Solvent :  $\text{CDCl}_3$

**Example 237 :** 4-Benzyl-7-cyano-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

10.8 g (27.1 mmol) of 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 164) in 100 ml of N-methylpyrrolidinone (NMP) are introduced into a 500 ml round-bottomed flask fitted with a stirring system, a condenser and a nitrogen inlet. 4.4 g (49 mmol) of cuprous cyanide are added and the mixture is then heated for 12 hours under nitrogen with stirring. The solvent is removed by evaporation under vacuum; the residue is stirred in a mixture of methylene chloride and 2N aqueous ammonia, the insoluble material is removed by filtration and the phases are then separated by settling. The organic phase is washed with saturated NaCl solution, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give 24.0 g of crude product. This product is purified by chromatography on a column of silica, eluting with a 65 ethyl acetate / 35 cyclohexane mixture. The TLC-pure fractions are combined and evaporated under vacuum: 8.4 g of the compound of Example 15 237 are obtained.

Yield = 90%.

m.p. (Tottoli) = 212-214°C

$^1\text{H}$  NMR  $\delta$  (ppm) : 2.9 (s, 6H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.5 (m, 2H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)

20 Solvent : DMSO

**Example 238 :** 4-Benzyl-7-carboxy-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

5.0 g (13.5 mmol) of 4-benzyl-7-cyano-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one suspended in 100 ml of 16 N hydrochloric acid solution are placed in a 250 ml round-bottomed flask and the mixture is then refluxed for 3 hours with stirring. After cooling, the precipitate is filtered off, washed several times with water, dried and purified by chromatography on a column of silica, eluting with a 97  $\text{CH}_2\text{Cl}_2$  / 3  $\text{CH}_3\text{OH}$  mixture to give 2.3 g of the TLC-pure compound of Example 238.

30 Yield = 44%

m.p. (Tottoli) = 335-337°C

$^1\text{H}$  NMR  $\delta$  (ppm) : 1.9 (s, 4H) ; 3.4 (s, 4H) ; 5.3 (s, 2H) ; 7.3 (m, 3H) ; 7.4 (m, 2H) ; 8.2 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

Solvent : DMSO

**Example 239 : 7-Bromo-4-[(4-methoxycarbonylmethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

0.8 g (1.65 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example 56) and 0.25 g of potassium carbonate are suspended in 10 ml of DMF. 0.26 g (1.82 mmol) of methyl iodide is added and the mixture is then heated at 80°C for 2 hours with stirring. The solvent is evaporated off under vacuum and the residue is taken up in water which is extracted 3 times with ethyl acetate; the combined organic phases are washed with saturated sodium chloride solution, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent is then evaporated off under vacuum to give 0.7 g of crude product.

10 This product is purified by chromatography on a column of silica, eluting with a 99 CH<sub>2</sub>Cl<sub>2</sub> / 1 CH<sub>3</sub>OH mixture. 0.5 g of TLC-pure product is obtained.

Yield = 61%

m.p. (Tottoli) = 161-162°C [C<sub>2</sub>H<sub>5</sub>OH]

15 <sup>1</sup>H NMR δ (ppm) : 2 - 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.6 (s, 2H) ; 3.7 (s, 3H) ; 5.45 (s, 2H) ; 7.2 (d, 2H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

**Example 240 : 7-Bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

**240-1/ 7-Bromo-4-[(4-chloroformylmethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

0.85 g (1.76 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Example XX) is placed in 85 ml of dry chloroform. The mixture is stirred under a stream of nitrogen, followed by addition of 0.42 g (3.52 mmol) of thionyl chloride while maintaining the temperature below +5°C. After 1 h 30 min, the reaction is virtually complete and the acid chloride precipitates out in the form of crystals. This solution is used for the next step without further purification.

30 **240-2/ 7-Bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.**

The solution obtained in Example 240-1 is added slowly, while maintaining the temperature < +5°C, to a solution, cooled to 0°C, of 0.6 g (8.8 mmol) of methylamine hydrochloride and 1.06 g of triethylamine in 85 ml of acetone. Stirring is then continued at 35 0°C for 15 minutes, after which the solution obtained is concentrated under vacuum. The residue is dissolved in methylene chloride, the organic phase is washed twice with water, dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent is evaporated off under vacuum and 1.0 g of crude product is thus recovered. This product is chromatographed on a column of silica, eluting with a

96 CH<sub>2</sub>Cl<sub>2</sub> / 4 CH<sub>3</sub>OH mixture to give 0.4 g which is recrystallized from ethanol. After drying, 0.27 g of pure compound is obtained.

Yield = 31%

m.p. (Tottoli) = 240°C

5 TLC (92CH<sub>2</sub>Cl<sub>2</sub> / 8CH<sub>3</sub>OH) : R<sub>f</sub> = 0,5

<sup>1</sup>H NMR δ (ppm) : 1.95 - 2.1 (m, 4H) ; 2.7 (d, 3H) ; 3.35 - 3.45 (m, 4H) ; 3.5 (s, 2H) ; 5.3 - 5.5 (m, 3H) ; 7.15 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

10 The compounds (I) of Examples 241 to 243 (Table 6) are prepared according to the process of Example 240.

TABLE 6

| Compound No. | R  | NR <sub>4</sub> R <sub>5</sub>  | Yield (%) | m.p. (°C) |
|--------------|--|---|-----------|-----------|
| 241          | 4-(NH <sub>2</sub> COCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CH |    | 38        | 268       |
| 242          | 4-(Me <sub>2</sub> NCOCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> C |   | 74        | 202       |
| 243          | 4-(HONHCOCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> C              |  | 47        | 229       |

15

- Compound 241 :

<sup>1</sup>H NMR δ (ppm) : 2.7 (s, 6H) ; 3.2 (s, 2H) ; 5.1 (s, 2H) ; 6.7 (s, 1H) ; 7.05 (d, 2H) ; 7.2 (m, 3H) ; 7.95 (m, 1H) ; 8.05 (d, 1H) ; 8.15 (s, 1H)

Solvent : DMSO

20

- Compound 242 :

<sup>1</sup>H NMR δ (ppm) : 2 - 2.15 (m, 4H) ; 2.9 (s, 3H) ; 2.95 (s, 3H) ; 3.35 - 3.45 (m, 4H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.15 (d, 2H) ; 7.65 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

25

- Compound 243 :

<sup>1</sup>H NMR δ (ppm) : 1.95 - 2.1 (m, 4H) ; 3.3 (s, 2H) ; 3.3 - 3.4 (m, 4H) ; 5.3 (s, 2H) ; 7.25 (d, 2H) ; 7.45 (d, 2H) ; 8.15 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1H) ; 8.8 (s, 1H) ; 10.7 (s, 1H)

Solvent : DMSO

30

**Example 244** : 7-Methyl-4-(4-cyanobenzyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo-[4,3-a]quinazolin-5-thione.

244-1/ 7-Methyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-thione.

1.0g (4.1 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-

5 5-one in 70 ml of toluene is placed in a three-necked round-bottomed flask equipped with a stirring system, a condenser and a nitrogen-introduction system, and 3.3 g (8.2 mmol) of Lawesson's reagent are added in a single portion. The mixture is refluxed for 24 hours with stirring. After cooling, 30 ml of 5% hydrochloric acid solution are added and the mixture is then poured into 250 ml of methanol with stirring. 250 ml of cyclohexane are added and the insoluble material is removed by filtration. The acidic methanolic phase is separated out by settling and concentrated under vacuum, and the residue is taken up in ice and triturated therein several times. The insoluble material recovered in the form of a lacquer is dissolved in 10 ml of isopropanol; starting with the solution obtained, stirred for 30 minutes, the yellow crystals which precipitated are filtered off, washed with isopropanol

10 and then with ether and dried under vacuum. 0.98 g of product is obtained, which is used for the next step without further purification.

Yield = 80 %

244-2/ 4-(4-Cyanobenzyl)-1-(N,N-dimethylamino)-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-thione.

20 Starting with 0.5 g (1.93 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-thione (Example 244-2), using method B described in Example 3, and after recrystallization from ethanol, 0.29 g of the compound of Example 244 is obtained.

25 Yield = 40%

m.p. (Tottoli) = 236°C

<sup>1</sup>H NMR δ (ppm) : 2.9(s,6H) ; 3.7(s,2H) ; 5.45(s,2H) ; 7.25(m,2H) ; 7.7(m,2H) ; 7.85(m,1H) ; 8.2(d,1H) ; 8.5(s,1H)

Solvent : CDCl<sub>3</sub>

30 Compounds (I) of Examples 245 and 246 (Table 7) are prepared according to the process of Example 244.

TABLE 7

| Compound No. | X1                | R   | NR4RS                                | Yield (%) | m.p. (°C) |
|--------------|-------------------|---|--------------------------------------|-----------|-----------|
| 245          | 7-Br              | 4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | CH <sub>3</sub><br>N-CH <sub>3</sub> | 13        | 276       |
| 246          | 7-CH <sub>3</sub> | (E) (pyrid-3-yl)-CH=CHCH <sub>2</sub>             | CH <sub>3</sub><br>N-CH <sub>3</sub> | 26        | 133       |

- Compound 245 :

5      <sup>1</sup>H NMR δ (ppm) : 2.9 (s, 6H) ; 4.7 (s, 2H) ; 7.65 (d, 2H) ; 7.75 (d, 2H) ; 8.1 (m, 2H) ; 8.4 (d, 1H)

Solvent : DMSO

- Compound 246 :

10     <sup>1</sup>H NMR δ (ppm) : 2.5 (s, 3H) ; 3.0 (s, 6H) ; 4.25 (d, 2H) ; 6.45 (dt, 1H) ; 6.75 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (d, 1H) ; 7.7 (d, 1H) ; 7.9 (s, 1H) ; 8.4 (m, 2H) ; 8.6 (bs, 1H)

Solvent : CDCl<sub>3</sub>

**B. Intermediate compounds**

15     Particularly preferred embodiments of the intermediate compounds of the present invention can be prepared according to the examples which follow. However, a person skilled in the art may easily modify the procedures described below as a function of the desired intermediate.

20     Example 250

Intermediate 1 :

1,2,3,4-Tetrahydro-3-benzyl-6-bromo-4-oxo-2-thiaquinazoline from 5-bromoanthranilic acid.

25     150 g (694 mmol) of 5-bromo-2-aminobenzoic acid suspended in 1.5 l of acetic acid are placed in a reactor fitted with a stirrer, a condenser and a dropping funnel.

The mixture is heated to reflux with stirring, and 92 ml (103 g; 694 mmol) of benzyl isothiocyanate are then added slowly and uniformly via the dropping funnel.

After the end of the addition, the mixture is refluxed for a further 6 hours with stirring; 30     during this period, dissolution takes place gradually.

After cooling to room temperature, the solid which has precipitated is filtered off and washed with acetic acid.

The product obtained is dried under vacuum to 60°C to give 125.2 g of the TLC-pure expected compound (elution solvent : 99.2 CH<sub>2</sub>Cl<sub>2</sub> / 0.8 CH<sub>3</sub>OH ; R<sub>f</sub> = 0.9)

Yield = 52%

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are compatible with the expected structure.

5

Example 251

Intermediate 2 :

3,4-Dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one.

10 125.2 g (360 mmol) of 1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thiaquinazoline (Intermediate 1) suspended in 3.5 l of ethanol are placed in a reactor fitted with a stirrer and a condenser.

167.6 g (3.348 mmol) of hydrazine hydrate are added with stirring.

15 The suspension obtained is refluxed for 18 hours, during which dissolution takes place gradually.

After cooling to room temperature, about half of the solvent is evaporated off under vacuum and the residual solution obtained is left to stand in a bath of ice for 1 hour.

After filtering off the precipitate, washing with cold ethanol and then drying under vacuum at 60°C, 89.7 g of the TLC-pure expected compound are obtained (elution solvent :

20 99 CH<sub>2</sub>Cl<sub>2</sub> / 1 CH<sub>3</sub>OH ; R<sub>f</sub> = 0.1)

Yield = 72%

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are compatible with the expected structure.

Example 252

25 Intermediate 3 :

4-Benzyl-7-chloro-1-mercaptop-4H-[1,2,4]triazolo[4, 3-a]quinazolin-5-one

30 47.7 g (158 mmol) of 3,4-dihydro-3-benzyl-6-chloro-2-hydrazinoquinazolin-4-one (prepared in a similar manner to that of Intermediate 2) dissolved in 600 ml de pyridine are placed in a reactor fitted with a stirrer and a condenser.

25.3 g (158 mmol) of potassium xanthogenate are then added portionwise and the solution obtained is refluxed for 7 hours with stirring, during which a solid gradually precipitates out.

35 After leaving to stand at room temperature overnight, the precipitate is separated out by filtration and then redissolved in 1.5 litres of water.

The solution obtained is neutralized with acetic acid and the precipitate formed is then filtered off, washed with water to neutral pH and dried.

54.0 g of crude product are obtained, which product is used for the next step without further purification.

Yield  $\approx$  100%

5

Example 253

Intermediate 4 :

4-Benzyl-7-chloro-1-methylthio-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

10 A solution of 6.72 g of sodium hydroxide in 1200 ml of water is placed in a reactor fitted with a stirrer and dropping funnel, followed by addition of 57.0 g (166 mmol) of 4-benzyl-7-chloro-1-mercaptoptriazolo[4,3-a]quinazolin-5-one (Intermediate 3).

15.74 ml (166 mmol) of dimethyl sulphate are added with stirring at room temperature, over a period of 30 minutes. Stirring is continued for 7 hours.

15 After leaving to stand at room temperature overnight, the precipitate is filtered off, washed with water and then dried under vacuum.

51.2 g of crude solid are obtained, which product is used for the next step without further purification.

Yield = 100%

20

Example 254

Intermediate 5 : 4-Benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

51.0 g (143 mmol) of 4-benzyl-7-chloro-1-methylthiotriazolo[4,3-a]quinazolin-5-one (Intermediate 4) in a mixture of 1.5 l of chloroform and 0.9 l of water are placed in a reactor fitted with a stirrer, a dip tube and a condenser.

The mixture is cooled to 0°C with stirring, and a stream of chlorine is then bubbled through for 2 hours, while keeping the temperature below 10°C.

Introduction of chlorine is then stopped, the mixture is allowed to return to room temperature and stirring is then continued for 2 hours.

30 The 2 phases are separated by settling and the chloroform phase is dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum.

50.9 g of crude solid residue are obtained. This product is suspended in 400 ml of ethanol and the heterogeneous mixture is stirred for 30 minutes. The insoluble material is filtered off, washed with ethanol and dried at 50°C under vacuum to give 46.5 g of the TLC-pure expected compound (elution solvent : 99  $\text{CH}_2\text{Cl}_2$  / 1  $\text{CH}_3\text{OH}$  ;  $R_f = 0.50$ )

Yield = 94%

The proton and  $^{13}\text{C}$  NMR spectra are compatible with the expected structure.

Example 255

Intermediate 6 : 4-Benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

89.7 g (260 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one  
5 (Intermediate 2) suspended in 2.9 l of dry chloroform are placed in a 6 litre reactor fitted with a stirrer.

The suspension is cooled to 0°C on an ice bath, with stirring, followed by addition of 216 ml (192.5 g ; 1299 mmol) of triethyl orthoformate, which results in a slight rise in temperature (to 6°C).

10 8.2 ml of concentrated sulphuric acid are added in a single portion, while keeping the temperature below 5°C. The mixture is then stirred for 15 min at a temperature below 5°C and the ice bath is then removed; stirring is continued for a further 4 hours, during which a solid gradually precipitates out.

15 1.5 l of water and 0.7 l of chloroform are added, with stirring until completely distributed between the 2 phases, and the aqueous phase is then neutralized to pH 7 with sodium bicarbonate.

The organic phase is separated out by settling, washed with saturated NaCl solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum to give 91.3 g of the TLC-pure expected compound (elution solvent : 97 CH<sub>2</sub>Cl<sub>2</sub> / 3 CH<sub>3</sub>OH / 0.3 NH<sub>4</sub>OH ; R<sub>f</sub> = 0.5).

20 Yield = 99%

m.p. (Tottoli) = 237°C

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are compatible with the expected structure.

Example 256

Intermediate 7 :

4-Benzyl-1,7-dibromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one.

35 g (98.5 mmol) of 4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (Intermediate 6) suspended in 630 ml of chloroform and 11 ml of pyridine are placed in a 30 3 litre reactor equipped with a stirrer, a condenser and a dropping funnel.

16.4 ml (320 mmol) of bromine are then added at room temperature with stirring, over a period of 30 minutes.

35 After the end of the addition, stirring is continued at room temperature for 1 hour ; the reaction medium is then partitioned between 1 l of water and 1.5 l of chloroform and the heterogeneous mixture is stirred for 15 min.

The insoluble material is spin-filtered, washed with water to neutral pH and then triturated from ethanol.

Under drying under vacuum, at 50°C, a first fraction of 8.2 g of the TLC-pure expected compound is obtained (elution solvent : 99 CH<sub>2</sub>Cl<sub>2</sub> / 1 CH<sub>3</sub>OH ; R<sub>f</sub> = 0.6).

After separation of the chloroform phase, washing with sodium bicarbonate solution and then with water, drying (Na<sub>2</sub>SO<sub>4</sub>), evaporation of the solvent under vacuum and then 5 trituration of the residue from ethanol, filtration and drying of the solid at 50°C, 33.1 g of a second fraction of the expected compound, which is equivalent to the preceding fraction by TLC, are obtained.

Total yield (for the 2 fractions) = 96%

The <sup>1</sup>H NMR spectrum is compatible with the expected structure.

10

Example 257

Intermediate 8 : 1-Azepanyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

15 1.0 g (2.68 mmol) of 1-azepanyl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one is dissolved in 60 ml of tetrahydrofuran in a 150 ml round-bottomed flask equipped with a stirrer and a condenser.

2.0 g of ammonium formate are added, followed by 1.5 g of activated 10% palladium-on-charcoal.

The mixture is stirred and heated at the reflux point of the solvent for 5 hours.

20 After cooling, the suspension is filtered and the solvent is then evaporated off under vacuum to give 0.55 g of residual solid.

This product is chromatographed on a column of silica, eluting with a 97 CH<sub>2</sub>Cl<sub>2</sub> / 3 CH<sub>3</sub>OH mixture; the TLC-pure fractions are combined and concentrated under vacuum to give 0.42 g of solid residue.

25 Yield = 55%

m.p. (Tottoli) = 222 - 224°C

TLC (95CH<sub>2</sub>Cl<sub>2</sub> / 5CH<sub>3</sub>OH) : R<sub>f</sub> = 0.4

<sup>1</sup>H NMR δ (ppm) : 1.65-1.85 (m, 8H) ; 3.25 (m, 4H) ; 7.5 (t, 1H) ; 7.9 (t, 1H) ; 8.15 (d, 1H) ; 8.3 (d, 1H) ; 12.6 (m, 1H)

30 Solvent : DMSO

The compounds (I ; R = H) of Examples 258 to 262 (Table 8) are prepared according to the process of Example 257.

TABLE 8

| Compound No. | X1                | NR4R5 | Yield (%) | m.p. (°C) |
|--------------|-------------------|-------|-----------|-----------|
| 258          | 7-Br              |       | 96        | >290      |
| 259          | 8-CH <sub>3</sub> |       | 64        | -         |
| 260          | 8-                |       | 75        | -         |
| 261          | 7-Br              |       | 89        | >300      |
| 262          | 7-Br              |       | 90.5      | >300      |

Example 263

5 Intermediate 9 : 1-Azepanyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

10.0 g of 1-azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (24.5 mmol) and then 19.6 g (147 mmol) of dry aluminium chloride are suspended in 200 ml of anhydrous benzene.

10 The suspension is stirred and heated at 50°C in the absence of moisture.  
 After 1 hour 30 minutes, the reaction mixture is allowed to cool, ice is added and this mixture is then stirred vigorously for 30 minutes.  
 The precipitate obtained is spin-filtered, washed with water to neutrality and dried at 50°C to give 7.5 g of TLC-pure solid.

15 Yield = 96%  
 m.p. (Tottoli) : >300°C  
 TLC (95 CH<sub>2</sub>Cl<sub>2</sub> / 5 CH<sub>3</sub>OH) : R<sub>f</sub> = 0.35

19 <sup>1</sup>H NMR δ (ppm) : 1.65-1.9 (m, 8H) ; 3.3 (m, 4H) ; 7.95 (d, 1H) ; 8.05 (s, 1H) ; 8.3 (d, 1H) ; 12.8 (m, 1H)

TABLE 9

| Compound No. | X1                | NR4R5 | m.p. (°C) |
|--------------|-------------------|-------|-----------|
| 264          | H                 |       | 283       |
| 265          | 7-CH <sub>3</sub> |       | 298       |
| 266          | 7-CH <sub>3</sub> |       | >300      |
| 267          | 7-CH <sub>3</sub> |       | -         |
| 268          | 7-OH              |       | 295       |
| 269          | 7-CN              |       | >300      |
| 270          | 7-CN              |       | -         |

Example 271

5    Intermediate 10 : 1-Amino-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5.0g (14.5 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazinoquinazolin-4-one (prepared according to Example XX) suspended in 150 ml of dry methanol are placed in a 500 ml reactor fitted with a stirring system, a condenser equipped with a potassium hydroxide guard tube, a dip thermometer and a nitrogen inlet. 1.62g (15.3 mmol) of cyanogen bromide are added and the heterogeneous mixture is stirred for 1 hour at room temperature and then refluxed for 5 hours. After cooling, saturated aqueous sodium bicarbonate solution is added dropwise, with vigorous stirring, to pH 8. The insoluble solid is filtered off, washed several times with water and dried under vacuum to give 4.9 g of crude product.

This product is triturated from 100 ml of methanol and the insoluble fraction is separated out by filtration, washed with methanol and dried under vacuum. 4.6g of TLC-pure product are obtained. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are compatible with the expected structure.

20    Yield = 86.5%

m.p. (Tottoli) = 287°C

TLC (95 CH<sub>2</sub>Cl<sub>2</sub> / 5 CH<sub>3</sub>OH 5) : R<sub>f</sub> = 0.5

5 **Evaluation of the *in vitro* activity of the preferred compounds of the invention**

**Inhibition of phosphodiesterase**

10 The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC<sub>50</sub> (concentration required to inhibit 50% of the enzymatic activity).

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from a cell line U937 of human origin according to the method adapted from T.J. Torphy et al., 1992, J.Pharm.Exp. Ther. 263 : 1195-1205.

15 The other types of phosphodiesterase are obtained from partial purification by FPLC on a Mono Q column (anion exchange column) according to a method adapted from Lavan B. E., Lakey T., Houslay M. D. Biochemical Pharmacology, 1989, 38(22), 4123-4136., and Silver P.J et al., 1988, Eur.J. Pharmacol. 150 : 85-94, either from cell lines of human origin for PDE1 (TPH1 monocyte line) and PDE5 (MCF7 line obtained from an 20 adenocarcinoma), or from dog aorta for PDE3, or, for human PDE3A, from cloning genes in SF21 insect cells into baculoviruses, according to the method adapted from Luckow, V. A. et al., 1991 in Recombinant DNA Technology&Applications., eds. Prokop, Bajpai, R.K.&Ho,C.S., pp 97-152.

25 The measurement of the enzymatic activity of the various types of PDE, and in particular the PDEs 4, is carried out according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

For the determination of the IC<sub>50</sub>, the enzymatic activity is measured in the presence of the inhibitor over a range of concentrations from 0.1 μM to 100 μM.

30 The table which follows illustrates the inhibitory activity of PDE4 on an enzyme preparation obtained from the U937 line.

| Compound No. | IC <sub>50</sub> (μM) | Compound No. | IC <sub>50</sub> (μM) | Compound No. | IC <sub>50</sub> (μM) |
|--------------|-----------------------|--------------|-----------------------|--------------|-----------------------|
| 1            | 0.054                 | 59           | 0.090                 | 190          | 0.19                  |
| 3            | 0.079                 | 60           | 0.050                 | 218          | 0.048                 |
| 11           | 0.080                 | 61           | 0.011                 | 223          | 0.012                 |
| 13           | 0.060                 | 62           | 0.053                 | 224          | 0.075                 |

| Compound No. | IC <sub>50</sub> (μM) | Compound No. | IC <sub>50</sub> (μM) | Compound No. | IC <sub>50</sub> (μM) |
|--------------|-----------------------|--------------|-----------------------|--------------|-----------------------|
| 20           | 0.04                  | 75           | 0.078                 | 227          | 0.028                 |
| 22           | 0.41                  | 76           | 0.070                 | 229          | 0.080                 |
| 32           | 0.053                 | 78           | 0.038                 | 230          | 0.002                 |
| 34           | 0.056                 | 79           | 0.14                  | 231          | 0.00027               |
| 35           | 0.020                 | 80           | 0.073                 | 233          | 0.18                  |
| 37           | 0.015                 | 81           | 0.016                 | 234          | 2.69                  |
| 40           | 0.014                 | 83           | 0.012                 | 239          | 0.005                 |
| 41           | 0.018                 | 85           | 0.041                 | 240          | 0.013                 |
| 42           | 0.024                 | 89           | 0.027                 | 242          | 0.011                 |
| 43           | 0.030                 | 92           | 0.030                 | 243          | 0.028                 |
| 44           | 0.090                 | 94           | 0.029                 | 246          | 0.041                 |
| 46           | 0.090                 | 96           | 0.058                 |              |                       |
| 47           | 0.050                 | 98           | 0.029                 |              |                       |
| 48           | 0.025                 | 102          | 0.060                 |              |                       |
| 49           | 0.080                 | 103          | 0.039                 |              |                       |
| 50           | 0.035                 | 104          | 0.077                 |              |                       |
| 51           | 0.027                 | 164          | 0.090                 |              |                       |
| 52           | 0.030                 | 186          | 0.090                 |              |                       |
| 57           | 0.014                 | 189          | 0.078                 |              |                       |

Examination of the results in the above table shows that the preferred products of the invention tested in the trial inhibit the enzyme PDE4 *in vitro* effectively.

5

Inhibition of the production of TNFα by human leukocytes stimulated by lipopolysaccharide

10 The aim of this test is to evaluate the capacity of the compounds of the invention to inhibit the production of TNFα (tumor necrosis factor-α) by human leukocytes in the presence of a high concentration of human serum (75%). The reason for this is that it is found that many compounds having the capacity to inhibit phosphodiesterase 4 in enzymatic or cell tests no longer have this capacity when the test is carried out in human blood. The test described here is based on the use of human leukocytes cultured in 75% human serum. It has previously 15 been documented that these conditions mimic the situation observed when the assay of TNFα is carried out in human blood.

The test compounds are dissolved at 20 mM (occasionally 6 mM) in DMSO. 100  $\mu$ l of DMSO are distributed in 7 wells of a 96-well microplate (wells B to H). 150  $\mu$ l of the solution of compounds are placed in the wells of line A. 50  $\mu$ l are then sequentially transferred 7 times. 20  $\mu$ l of these serial dilutions of compounds are sequentially transferred twice into wells containing 180  $\mu$ l of RPMI 1640 (Gibco). 50  $\mu$ l of these dilutions are then transferred into wells into which the cells will be added.

5 Each test comprises a series of eight wells without LPS (100% inhibition), eight wells with LPS (0% inhibition) and a series of dilutions of Rolipram in order to be able to compare the tests with each other and thus evaluate their variability.

10 An ampule of leukocytes is thawed on a water bath (37°C), its contents are transferred into a 15 ml tube containing 10 ml of RPMI supplemented with 5% human serum (RPMI-5% HS). The cells are sedimented (800  $\times$  g, 6 minutes, 4°C), taken up in 10 ml of the same medium and counted by dilution in a solution of Trypan blue. After centrifugation 15 (800  $\times$  g, 6 minutes, 4°C), the cells are taken up at a proportion of  $2 \times 10^6$ /ml in human serum.

100  $\mu$ l of cells are added to 50  $\mu$ l of the various dilutions of compounds. The plates are then incubated for 30 minutes at 37°C, after which 50  $\mu$ l of a 4  $\mu$ g/ml solution of LPS prepared in human serum are added. The plates are incubated overnight at 37°C.

20 After incubation for 15-18 hours, 90  $\mu$ l of culture supernatant are removed and transferred into round-bottomed microplate wells. The presence of TNF $\alpha$  is then evaluated by ELISA (Pharmingen), using 50  $\mu$ l of supernatant. The protocol described by the manufacturer is applied rigorously.

25 The results obtained for some of the preferred compounds of the present invention are illustrated in the table which follows.

| Compound | Inhibition (human leukocytes)<br>$IC_{50}$ $\mu$ M |
|----------|--|
| 3        | 3.4  |
| 104      | 8.1  |
| 94       | 6.3  |
| 101      | 8.6  |
| 85       | 6.8  |
| 98       | -  |
| 79       | 5.2  |
| 91       | -  |
| 93       | 4.3  |
| 103      | 10.7   |
| 46       | -  |
| 35       | -  |

Evaluation of the *in vivo* activity of the compounds of the invention

5

*in vivo* TNF $\alpha$  model in Wistar rats

TNF $\alpha$  is a cytokine which plays a central role in the mechanisms of inflammation. Its production can be induced by an injection of lipopolysaccharide (LPS). It has been shown that the increase in intracellular cAMP, produced in particular by PDE4 inhibitors, decreases the production of TNF $\alpha$  in *in vitro* and *in vivo* models. Thus, what is involved here is to quantify *in vivo* the anti-inflammatory potential of the compounds of the invention, administered orally (p.o.), by measuring the inhibition of the production of TNF $\alpha$  in the plasma of rats, these rats having received an intraperitoneal (i.p.) injection of lipopolysaccharide (LPS). For the treatment with the compounds of the invention or the vehicle, the latter are administered orally to male Wistar rats, 30 min before the injection of LPS. The rats are sacrificed 90 min after the stimulation with LPS, the blood is collected over EDTA and the concentration of TNF $\alpha$  is measured in each sample of plasma. The results obtained for some of the compounds of the present invention are given in the table below.

| Compound | % inhibition at 10 mg/kg |
|----------|--------------------------|
| 3        | - 98 %                   |
| 104      | - 94 %                   |
| 94       | - 87 %                   |
| 101      | - 80 %                   |
| 85       | - 77 %                   |
| 98       | - 75 %                   |
| 79       | - 72 %                   |
| 91       | - 70 %                   |
| 93       | - 67 %                   |
| 103      | - 64 %                   |
| 46       | - 58 %                   |
| 35       | - 51 %                   |

5 References

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Prabhakar, U., Lipshutz, D., O'Leary Barthus, J., Slivjak, J., Smith III E. F., Lee, J. C. and 10 Esser K. M. (1994). Characterization of cAMP-dependent inhibition of LPS-induced TNF $\alpha$  production by rolipram, a specific phosphodiesterase IV (PDE IV) inhibitor. Int. J. Immunopharmacol., 16 (10), 805-816.

15 **Model of eosinophilia in rats**

The studies carried out using this experimental model are designed to evaluate the inhibitory action of the compounds of the invention on the afflux in inflammatory cells and in particular of eosinophils in the lumen of the tracheobronchial tree of rats. Eosinophils play a major role in the physiopathology of asthma in man by releasing into the pulmonary 20 parenchyma pro-inflammatory mediators such as leukotrienes, specific proteins and

enzymes (ECP, EPO, MBP) and cytokines. The massive recruitment of this cell type in the aerial pathways of asthmatics leads to a gradual degradation of the pulmonary tissue, explaining the bronchial hyperreactivity, the chronic aspect of the condition and the exacerbations in the absence of treatment. This model uses Brown Norway rats, which  
5 have the particular feature of producing, like atopic patients, levels of immunoglobulin E (IgE) in response to sensitization with an antigen. The protocol used involves two sensitizations with ovalbumin with an interval of fourteen days, followed by a challenge seven days later with an ovalbumin aerosol. 48 hours after the antigenic challenge, the animals undergo bronchoalveolar lavage under anaesthesia in order to collect the infiltrate  
10 of inflammatory cells in the lungs. These cells are then counted and differentiated according to the morphological criteria. The products of the invention are administered orally, 1 hour before the antigenic challenge. Most of the preferred compounds of the present invention tested in this model also demonstrated excellent activity.

15 **References**

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20 **Model of neutrophilia in mice**

The studies carried out using this experimental protocol are designed to evaluate the modulatory action of the compounds of the invention on the afflux of pro-inflammatory cells (early phase) in the lumen of the tracheobronchial tree of mice. This cell afflux follows a stimulation mimicking a bacterial infection (bacterial lipopolysaccharide or LPS). This  
25 inflammatory early stage is the result of a combination of events, the main ones being the synthesis and release of stimulatory factors (TNF $\alpha$ i) and chemotactic factors (IL-8ii), the increase in vascular permeability in the tracheobronchial microcirculation and the infiltration of polymorphonuclear neutrophils concomitant with the exudation of the plasma proteins into the pulmonary tissues.  
30 This pathological process is found in chronic obstructive pulmonary disease, in which the neutrophils, in concert with the macrophages, play a key role in establishing the amplification of the recruitment of the neutrophils themselves, but also in the destructuring of the pulmonary tissues (decline in the pulmonary functions), the hypersecretion of tracheobronchial mucus (engorgement of the aerial pathways), the tissue inflammation  
35 (release of inflammatory mediators and free radicals) and the increase in the basal tonus of the pulmonary smooth muscle fibres (chronic difficulty in breathing). Some of the compounds of the examples showed activity in this model.

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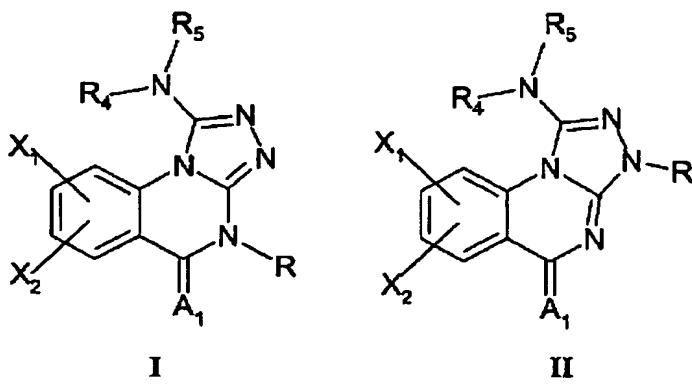
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Claims

1. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones of formula I or II:

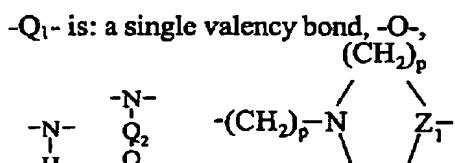


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I and II being positional isomers of the group  $\text{R}$  on nitrogens 3 or 4, in which:

- $\text{A}_1$  is O or S;
- $\text{X}_1$  and  $\text{X}_2$ , which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
  - lower alkyl, lower alkoxy or  $-\text{S}(\text{O})_m\text{R}_8$  in which  $m$  is 0, 1 or 2 and  $\text{R}_8$  is a lower alkyl, which are optionally substituted with one or more halogen atoms,
  - $-\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$  in which:

10



15

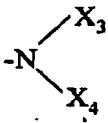
15, in which  $p$  is an integer which can range from 0 to 3, and  $\text{Z}_1$  is CH, N, O or S,

$-\text{Q}_2-$  is:

a)  $-(\text{CH}_2)_q-$ ,  $q$  being equal to 0, 1, 2, 3, or 4, or

b)  $-(\text{CH}_2\text{-CH}_2\text{-O})_r-$ ,  $r$  being equal to 2, 3 or 4, and

$-\text{Q}_3$  is:  $-\text{H}$ ,  $-\text{OH}$ , lower alkoxy,  $-\text{O-CO-X}_3$   $-\text{NHX}_3$  or



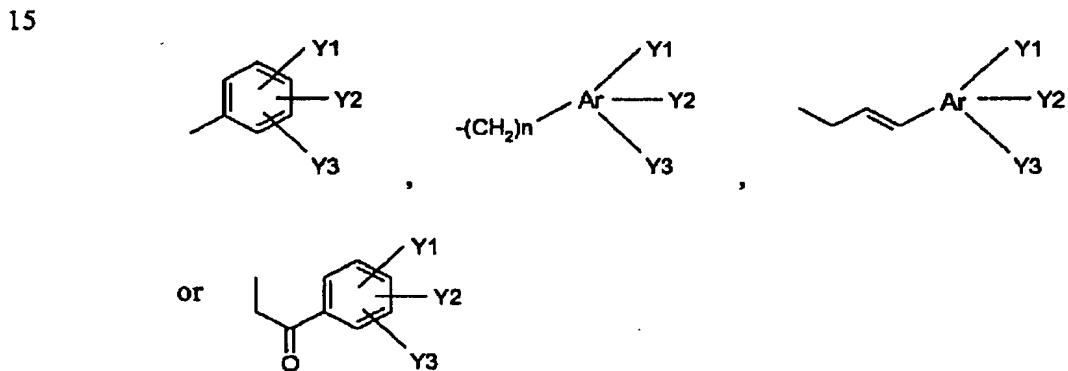
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in which  $\text{X}_3$  and  $\text{X}_4$ , which may be identical or different, represent a lower alkyl group, it being possible for  $\text{X}_3$  and  $\text{X}_4$  to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N,

- $-\text{NH}-\text{R}_1$  in which  $\text{R}_1$  represents a lower alkyl group, optionally substituted with one or more groups chosen from halogen, hydroxyl, cyano, lower alkoxy and  $-\text{CO}-\text{Q}_1-\text{Q}_2-\text{Q}_3$ , or
- $-\text{NR}_2\text{R}_3$  in which  $\text{R}_2$  and  $\text{R}_3$ , which may be identical or different, represent a lower alkyl, optionally substituted with one or more hydroxyl, halogen, cyano, lower alkoxy or  $-\text{CO}-\text{Q}_1-\text{Q}_2-\text{Q}_3$  groups, it being possible for  $\text{R}_2$  and  $\text{R}_3$  to be linked to form a ring, comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy and  $-\text{CO}-\text{Q}_1-\text{Q}_2-\text{Q}_3$ ;

5

- $\text{R}$  represents:
  - lower alkyl, lower alkenyl, lower alkynyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl optionally substituted with a lower alkyl, lower alkoxy,



20 hydroxyl, halogen or amino group,

in which:

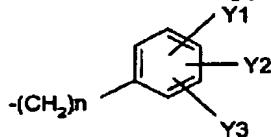
- $\text{n}$  is an integer from 1 to 5,
- $\text{Ar}$  is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N,
- $\text{Y}_1$ ,  $\text{Y}_2$  and  $\text{Y}_3$ , which may be identical or different, represent:
  - hydrogen, hydroxyl, mercapto, amino, nitro, halogen,  $\text{NHR}_1$ ,  $\text{NR}_2\text{R}_3$ ,  $-(\text{CH}_2)_s\text{CN}$ , or  $-(\text{CH}_2)_s\text{CO}-\text{Q}_1-\text{Q}_2-\text{Q}_3$  in which  $s$  is an integer from 0 to 6;
  - lower alkyl, lower alkoxy or  $-\text{S}(\text{O})_m\text{R}_8$  in which case  $m$  is 0, 1 or 2 and  $\text{R}_8$  is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms; and

-  $\text{R}_4$  and  $\text{R}_5$ , represent:

- lower alkyl when R<sub>4</sub> and R<sub>5</sub> are identical, aralkyl, cycloalkyl or cycloalkyl-alkyl, when R<sub>4</sub> and R<sub>5</sub> are different,
- lower alkyl, it being possible for R<sub>4</sub> and R<sub>5</sub> to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, it also being possible for two of the atoms in the ring thus formed to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms;

5                    optionally the racemic forms thereof and the isomers thereof, as well as the pharmaceutically acceptable salts thereof.

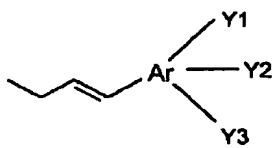
10                    2. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to Claim 1, in which:  
15                    A<sub>1</sub> represents an oxygen atom;  
X<sub>1</sub> represents a hydrogen atom and X<sub>2</sub> is a halogen, amino, lower alkyl, hydroxyl or -NHR<sub>1</sub> group, R<sub>1</sub> being as defined above,  
20                    R represents:  
- a lower alkyl, lower alkenyl, arylalkynyl, 2-, 3- or 4-pyridylalkyl group optionally substituted on the pyridine nucleus with a lower alkyl, a halogen or a hydroxyl;



25                    in which:

- n is an integer from 1 to 3,
- Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y<sub>1</sub> and Y<sub>2</sub> each represent a hydrogen atom and Y<sub>3</sub> represents a lower alkoxy group, an amino group, NHR<sub>1</sub>, NR<sub>2</sub>R<sub>3</sub>, nitro, hydroxyl, a group -(CH<sub>2</sub>)<sub>s</sub>CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, a group (CH<sub>2</sub>)<sub>s</sub>-CN in which s, Q<sub>1</sub>, Q<sub>2</sub>, and Q<sub>3</sub> are as defined above, or a lower alkyl group optionally substituted with one or more halogen atoms, the position which is particularly preferred for the substituent Y<sub>3</sub> being position 4, or
- Y<sub>1</sub> represents a hydrogen atom and Y<sub>2</sub> and Y<sub>3</sub>, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group, or

30



in which:

- Ar is as defined above;
- Y1, Y2 and Y3 each represent a hydrogen atom, or

5      - Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen;

R<sub>4</sub> and R<sub>5</sub> represent:

- lower alkyl when R<sub>4</sub> and R<sub>5</sub> are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R<sub>4</sub> and R<sub>5</sub> are different,

10     lower alkyl, it being possible for R<sub>4</sub> and R<sub>5</sub> to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, it being possible for two of the atoms of the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

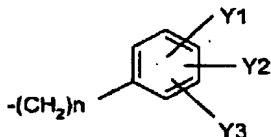
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3. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to Claim 1 or 2, in  
20     which:

X<sub>1</sub> represents a hydrogen atom,

X<sub>2</sub> represents a halogen, amino, lower alkyl, hydroxyl or -NHR<sub>1</sub> group;

25     R represents:

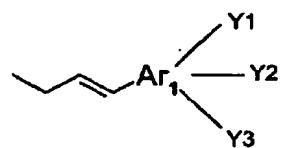


in which:

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-trimethoxy,

5            - Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy, amino,  $\text{NHR}_1$ ,  $\text{NR}_2\text{R}_3$ , nitro, or hydroxyl group, a lower alkyl group optionally substituted with one or more halogen atoms, a group  $-(\text{CH}_2)_s\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$  in which s is 0 or 1,  $\text{Q}_1$  is O, -NH- or a valency bond,  $\text{Q}_2$  is  $-(\text{CH}_2)_q$ , q being equal to 0 1, 2, 3 or 4 and  $\text{Q}_3$  is H, OH or  $-\text{NX}_3\text{X}_4$  in which  $\text{X}_3$  and  $\text{X}_4$  are as defined above, a group  $(\text{CH}_2)_s\text{-CN}$  in which s is 0 or 1, the position particularly preferred for the substituent Y3 being position 4 or

10            - Y1 represents a hydrogen atom and Y2 and Y3, which may be identical or different, represent a hydroxyl, halogen or lower alkoxy group; or



in which:

15            -  $\text{Ar}_1$  is an aromatic ring comprising 6 atoms which can include a nitrogen atom in position 2, 3 or 4 and preferably in position 3;

20            - Y1, Y2 and Y3 each represent a hydrogen atom, or

25            - Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy group or a halogen group when  $\text{Ar}_1$  does not comprise a nitrogen atom; and

30            R<sub>4</sub> and R<sub>5</sub>, represent:

35            - lower alkyl, when R<sub>4</sub> and R<sub>5</sub> are identical, aralkyl, cycloalkyl or cycloalkylalkyl when R<sub>4</sub> and R<sub>5</sub> are different,

40            - lower alkyl, it being possible for R<sub>4</sub> and R<sub>5</sub> to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally substituted with a lower alkyl, a hydroxyl or a lower alkoxy or bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, it being possible for two of the atoms of the ring thus formed also to form part of another ring chosen from phenyl and heteroaryl comprising from 4 to 8 atoms including 1 to 4 hetero atoms.

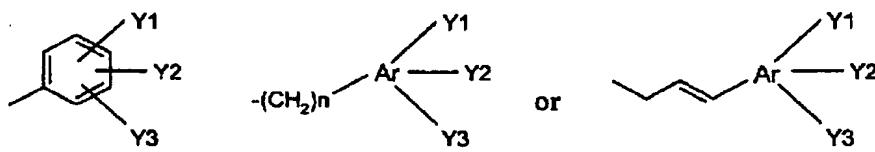
4. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to any one of Claims 1 to 3, in which:

35            - the halogen group is chosen from F, Cl, Br and I,

- the lower alkyl group is a linear or branched group containing from 1 to 6 carbon atoms,
- the lower alkoxy group is a linear or branched group containing from 1 to 5 carbon atoms,
- 5 - the lower alkylthio group is a linear or branched group containing from 1 to 5 carbon atoms,
- the lower alkenyl group contains from 3 to 6 carbon atoms,
- the lower alkynyl group contains from 3 to 6 carbon atoms,
- the 2-, 3- or 4-pyridylalkyl group comprises an alkyl containing 1 to 5 carbon
- 10 atoms,
- the aryl group contains from 5 to 8 carbon atoms,
- the aralkyl group comprises an alkyl containing from 1 to 6 carbon atoms,
- the cycloalkyl group contains from 3 to 8 carbon atoms,
- the cycloalkylalkyl group comprises an alkyl containing from 1 to 6 carbon
- 15 atoms,
- the lower alkyl, lower alkoxy or lower alkylthio groups substituted with one or more halogen atoms are chosen from the groups  $-(CH_2)_p-CF_3$ ,  $-O-(CH_2)_p-CF_3$  or  $-S-(CH_2)_p-CF_3$ , in which p is an integer from 0 to 3.

20 5. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to Claim 1, in which:

- $A_1$  is O or S;
- $X_1$  and  $X_2$ , which may be identical or different, represent:
  - hydrogen, hydroxyl, halogen, amino, nitro, mercapto, cyano, carboxyl,
  - lower alkyl, lower alkoxy or  $-S(O)_mR_3$  in which m is 0, 1 or 2 and  $R_3$  is a lower alkyl, which are optionally substituted with one or more halogen atoms;
- 25 - R represents:



30

in which:

- n is an integer from 1 to 5,
- Ar is an aromatic ring comprising 5 or 6 atoms including from 0 to 3 hetero atoms chosen from O, S and N

- Y1, Y2 and Y3, which may be identical or different, represent:
  - hydrogen, hydroxyl, mercapto, amino,  $\text{NHR}_1$ ,  $\text{NR}_2\text{R}_3$ , nitro, halogen,  $-(\text{CH}_2)_s\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$ , or  $-(\text{CH}_2)_s\text{-CN}$  in which s is an integer from 0 to 6;
  - lower alkyl, lower alkoxy or  $-\text{S}(\text{O})_m\text{R}_8$  in which m is 0, 1 or 2 and  $\text{R}_8$  is a lower alkyl, it being possible for each to be optionally substituted with one or more halogen atoms;
- $\text{R}_4$  and  $\text{R}_5$ , which may be identical or different, represent:
  - lower alkyl, it being possible for  $\text{R}_4$  and  $\text{R}_5$  to be linked to form a saturated ring or a ring including one or more double bonds comprising one or more hetero atoms chosen from O, S and N and optionally bridged with a lower alkyl, gem-dialkylated or substituted with one or more groups chosen from hydroxyl, keto, lower alkyl, lower alkoxy, phenylalkyl and  $\text{CO-Q}_1\text{-Q}_2\text{-Q}_3$ .

10 6. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to Claim 5, chosen from the group comprising:

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to Claim 1, 2, 3 or 4, chosen from the group comprising:

1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5-[(1-(Azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

7-Chloro-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-chlorophenyl)allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-methoxyphenyl)allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)acetate

7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3,5-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-(3,5-dimethylisoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoroethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-hydroxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-diethylaminoethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenoxyethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenylsulphenylethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl (7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenylacetate

4-(7-Bromo-5-oxo-1-piperid-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetonitrile

7-Bromo-1-dimethylamino-4-(pyrid-3-ylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenylacetate

1-Azepan-1-yl-7-methyl-4-pyrid-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

7-Methyl-4-pyrid-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

7-Methyl-4-(3-pyrid-3-ylallyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

[4-(Dimethylaminomethyl-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]-acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

(4-Cyanobenzyl)dimethylamino-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

7-Hydroxy-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(4-methylbenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

Methyl 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-acetyl]-2-methoxybenzoate

1-(Azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-(Azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-benzonitrile

1-(Azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl]phenyl]acetic acid

1-(Azepan-1-yl)-7-bromo-3-(pyrid-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-((E)-3-phenylallyl)-1-piperid-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)benzoate

7-Bromo-3-(4-methoxybenzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)acetate

7-Bromo-1-dimethylamino-3-(4-hydroxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(Benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(3,5-dimethoxybenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl (7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenylacetate

7-Bromo-1-dimethylamino-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenylacetate

1-(Azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-8-methyl-3-((E)-3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1,8-Bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(butylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-azabicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-chloro-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(piperid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-phenylpiperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-(4-benzylpiperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyrid-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydropyrrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(4-Benzylpiperid-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(ethylmethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-acetamide

N-[5-Oxo-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl]acetamide

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(Aminodimethylamino-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-methanesulphonamide

4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxyacetamide

4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

4-Benzyl-7-(N,N-dimethylsulphonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a]-quinazolin-5-one

8. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to any one of Claims 1 to 4, chosen from the group comprising:

1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

7-Bromo-4-(4-nitrobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Phenyl 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)acetate

7-Bromo-4-(4-hydroxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chlorophenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[3-(4-methoxyphenyl)allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyrid-4-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-piperid-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl 4-(7-bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)benzoate

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetonitrile

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetic acid

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(Dimethylaminomethyloxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)phenyl]acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydroazepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)phenyl]acetic acid

4-Benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydropyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Aminobenzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-dimethylamino-4-((E)-3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxyacetamide

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

9. Triazolo[4,3-a]quinazolin-5-ones and/or -5-thiones according to any one of Claims 1 to 4, chosen from the group comprising:

7-Bromo-1-dimethylamino-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyrid-4-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methylbenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chlorobenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxybenzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(Piperid-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Methyl 4-(Bromodimethylamino-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoate

7-Bromo-1-dimethylamino-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenylprop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxybenzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyrid-3-ylallyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)benzonitrile

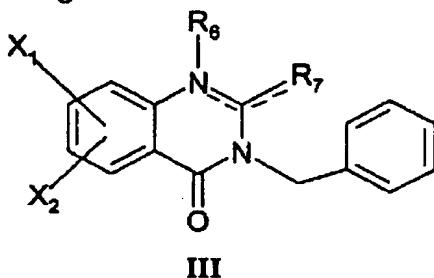
Methyl [4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl-methyl)phenyl]acetate

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methylacetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethylacetamide

1-Dimethylamino-7-methyl-4-(3-pyrid-3-ylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

**10. Intermediate compounds of general formula III:**



in which:

5

- $X_1$ ,  $X_2$  and  $A_1$  are as defined in Claim 1;
- the dashed lines represent optional double bonds;
- $R_6$  is hydrogen; and
- $R_7$  is S or hydrazino;

10 it being possible for  $R_7$  to be linked to the nitrogen in  $R_6$  to form a ring, particularly a

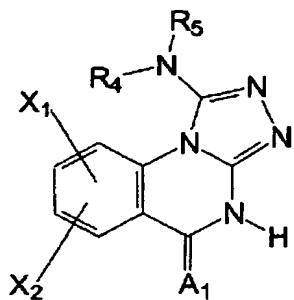
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triazole, optionally substituted with a lower thioalkyl, mercapto or halogen group, with the proviso that when R<sub>7</sub> is S or hydrazino and X<sub>1</sub> is hydrogen, halogen, alkyl group comprising from 1 to 3 carbon atoms, alkoxy group comprising 5 from 1 to 3 carbon atom or nitro, then X<sub>2</sub> is not hydrogen, halogen, alkyl group comprising from 1 to 3 carbon atoms, alkoxy group comprising from 1 to 3 carbon atom or nitro.

11. Intermediate compounds of general formula IV:

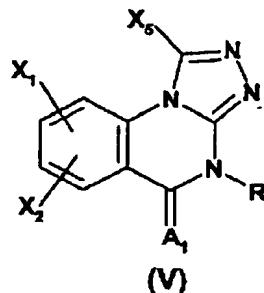
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IV

in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are as defined in Claim 1.

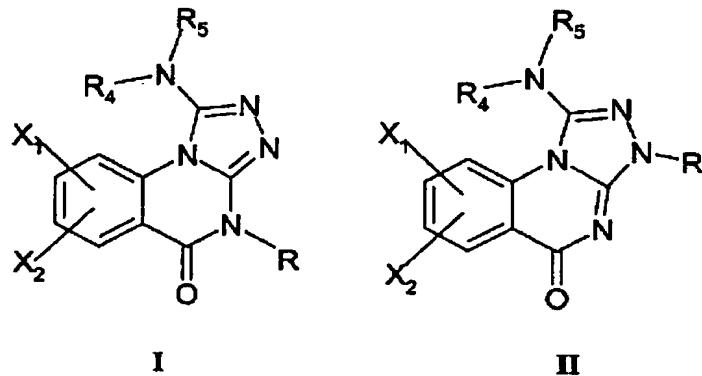
12. Intermediate compounds of general formula V:



5

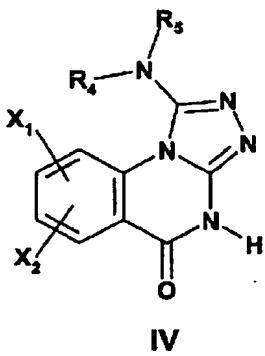
in which  $X_1$ ,  $X_2$ ,  $A_1$  and  $R$  are as defined in Claim 1 and  $X_5$  is a halogen, particularly F, Br or Cl,  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group.

10 13. Process for manufacturing the compounds of general formulae I and II:



in which  $X_1$ ,  $X_2$ ,  $R$ ,  $R_4$  and  $R_5$  are as defined in Claim 1,

15 the said process being characterized in that it comprises the reaction of a compound of general formula IV:



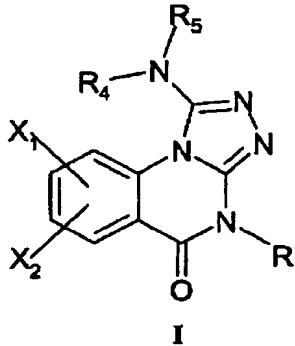
in which  $X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  are as defined in Claim 1,  
with a compound of general formula

5  $R-X'$

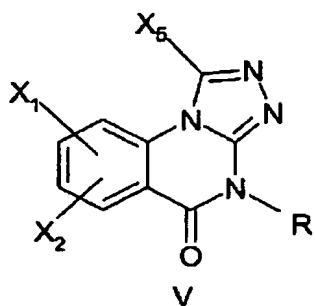
in which  $R$  is as defined above and  $X'$  is a halogen, particularly F, Br or Cl,  $-OCOX_7$  or  
 $-OSO_2X_7$  group in which  $X_7$  is a lower alkyl or aryl group;  
to give a mixture of the compounds of general formulae I and II, which are then optionally  
separated.

10

14. Process for manufacturing the compounds of general formula I:



in which  $X_1$ ,  $X_2$ ,  $R$ ,  $R_4$  and  $R_5$  are as defined in Claim 1,  
the said process being characterized in that it comprises the reaction of a compound of  
15 general formula V:

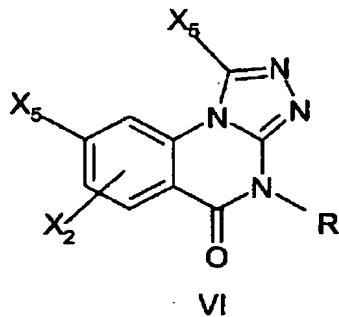


in which  $X_1$ ,  $X_2$  and  $R$  are as defined in Claim 1 and  $X_5$  is halogen, particularly F, Br or Cl, -OCOX<sub>7</sub>, -OSO<sub>2</sub>X<sub>7</sub> or -SO<sub>2</sub>X<sub>7</sub> group in which X<sub>7</sub> is a lower alkyl or aryl group; with a compound of general formula:



5 in which  $R_4$  and  $R_5$  are as defined in Claim 1,  
to give a compound of general formula I.

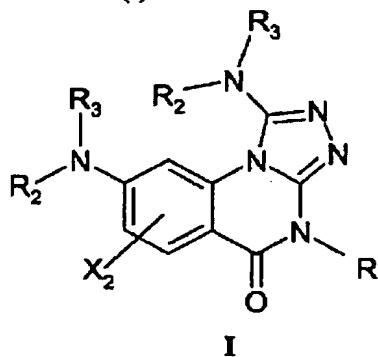
15. Process according to Claim 14, characterized in that when  $X_1$  is -NR<sub>2</sub>R<sub>3</sub> and -NR<sub>2</sub>R<sub>3</sub> and -NR<sub>4</sub>R<sub>5</sub> are identical, the compounds of formula I are obtained by reacting a  
10 compound of general formula VI:



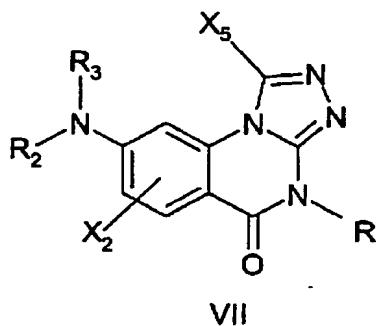
in which  $X_2$  and  $R$  are as defined in Claim 1 and  $X_5$  is as defined in claim 12  
with a compound of general formula:



15 in which  $R_2$  and  $R_3$  are as defined in Claim 1,  
to give a compound of general formula (I):



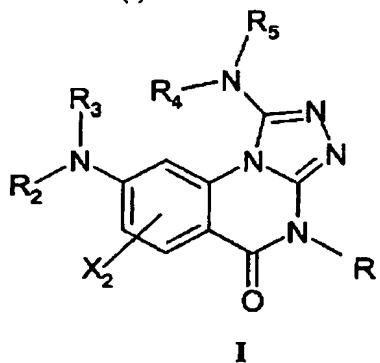
16. Process according to Claim 14, characterized in that when  $X_1$  is -NR<sub>2</sub>R<sub>3</sub> and -NR<sub>2</sub>R<sub>3</sub> and -NR<sub>4</sub>R<sub>5</sub> are different, the compounds of formula I are obtained by reacting a  
20 compound of general formula VII:



in which  $X_2$ ,  $R$ ,  $R_2$  and  $R_3$  are as defined in Claim 1 and  $X_5$  is as defined in claim 12, with a compound of general formula:



5 in which  $R_4$  and  $R_5$  are as defined in Claim 1,  
to give a compound of general formula (I):



17. Pharmaceutical composition comprising a compound according to any one of Claims 1  
10 to 9 and a pharmaceutically acceptable excipient .

18. Use of a compound according to any one of Claims 1 to 9 for the preparation of a  
medicinal product intended for treating a condition or complaint involving a treatment  
by inhibition of phosphodiesterases, and more particularly of PDE4.

15

19. Use according to Claim 18, characterized in that the condition is asthma.

20

20. Use according to Claim 18, characterized in that the condition is chronic bronchitis or  
acute pulmonary attack.

21. Use according to Claim 18, characterized in that the condition is atopic dermatitis.

22. Use according to Claim 18, characterized in that the condition is pulmonary  
hypertension.

23. Use according to Claim 18, characterized in that the condition is cardiac or pulmonary insufficiency.

5 24. Use according to Claim 18, characterized in that the condition is psoriasis.

25. Use according to Claim 18, characterized in that the condition is an inflammatory condition of the digestive system such as haemorrhagic rectocolitis or Crohn's disease.

10 26. Use according to Claim 18, characterized in that the condition is diabetes or a condition associated with a high level of TNF- $\alpha$ , such as acute respiratory distress syndrome or acute pancreatitis.

15 27. Use according to Claim 18, characterized in that the condition is benign hypertrophy of the prostate.

28. Use according to Claim 18, characterized in that the condition is chosen from rheumatoid arthritis and multiple sclerosis.

20 29. Use according to Claim 18, characterized in that the condition is chosen from depression, ischaemia-mediated neuronal attack and partial cerebral ischaemia.

30. Use according to Claim 18, characterized in that the condition is cancer, more particularly malignant tumours or chronic lymphoid leukaemia.

25 31. Use of a compound according to any one of Claims 1 to 9 to attenuate the development of tolerance or morphine-dependency phenomena.

30 32. Use of a compound according to any one of Claims 1 to 9 to reduce behavioural memory losses.

33. Use of a compound according to any one of Claims 1 to 9 to prevent premature labour.

35 34. Use according to Claim 18, characterized in that the condition is septicaemia or multiple organ failure syndrome.

35. Use according to Claim 18, characterized in that the condition is chronic obstructive pulmonary disease (COPD).

- 36. Use according to Claim 18, characterized in that the condition is emphysema.**
- 37. Use according to Claim 18, characterized in that the condition is allergic rhinitis.**
- 5 38. Use according to Claim 18, characterized in that the condition is congestive cardiac insufficiency.**
- 39. Use according to Claim 18, characterized in that the condition is osteoporosis.**

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